Open Access Library Journal
2025, Volume 12, e13706
ISSN Online: 2333-9721
ISSN Print: 2333-9705

Humoral Immunity in Pediatric Patients with Recurrent Infections: A Study in the Pediatric II Service of the "Ruíz y Páez" University Hospital Complex, Ciudad Bolívar, Bolívar State, Venezuela

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How to cite this paper: Gómez-Sifontes, A.E., Mejías-Pereira, E.E. and Tabata-Rodríguez, P.A. (2025) Humoral Immunity in Pediatric Patients with Recurrent Infections: A Study in the Pediatric II Service of the "Ruíz y Páez" University Hospital Complex, Ciudad Bolívar, Bolívar State, Venezuela. *Open Access Library Journal*, **12**: e13706.
https://doi.org/10.4236/oalib.1113706

Received: May 31, 2025
Accepted: August 8, 2025
Published: August 11, 2025

Abstract

Background: Infectious processes are the leading cause of pediatric consultation, and recurrent or severe infections may indicate primary immunodeficiencies (PIDs), which comprise more than 484 rare diseases affecting the immune response. The nature and severity of infections depend on the component of the immune system affected, with defects in humoral immunity being a frequent cause of severe respiratory infections. Evaluation of blood immunoglobulin (Ig) levels is essential for the identification of PIDs. However, the prevalence and specific immunoglobulin levels in this population still require further study in our region. Objective: To evaluate immunoglobulin levels (IgA, IgG, IgM) in pediatric patients with recurrent infections and to determine their relationship with possible primary immunodeficiencies (PID) in the Pediatrics Service II of the University Hospital Complex "Ruíz y Páez" of Ciudad Bolívar. Methods: A descriptive, prospective, cross-sectional study was performed on 30 pediatric patients with at least one alarm sign according to the Jeffrey Modell Foundation. Data included age, gender, type of infections, and serum immunoglobulin levels. Igs levels were analyzed and compared between groups. For the comparison of variables, an ANOVA was applied, considering as statistically significant those results with a confidence margin greater than 95% or a p-value less than 0.05. In addition, patients were classified into possible cases of PID, based on both immunoglobulin levels and clinical findings, following the diagnostic criteria established by the Society for Pediatric Immunology and clinical consensus. Diagnostic confirmation of PID was made by clinical evaluation, immunoglobulin analysis. Results: The most

frequent infections were pneumonia (n = 6) 20.00% and cutaneous abscesses n = 6 (20.00%). The distribution by gender was females (n = 18) 60.00% and (n = 12) males 40.00% with a mean age of 4.2 ± 1.8 years. Immunoglobulin levels presented the following means (± SD): IgA. 45.6 ± 12.3 mg/dL, with 10% of patients showing low levels (<5.0 mg/dL); IgG, 950 ± 150 mg/dL, within normal range in most; and IgM, 88.4 ± 24.5 mg/dL, with 6.67% of elevated levels. Low IgA levels were observed in cases of pneumonia (n = 3) 10.00%, a and otitis (n = 3) 10.00%, and elevated IgM levels in patients with skin abscesses (n = 2) 6.67%. Statistical comparison of immunoglobulin levels between groups revealed no significant differences ($p > 0.05$). Diagnosis of possible PID: 21 patients were identified with profiles suggestive of PID, in particular, selective IgA deficiency (n = 8) 38.10% and common variable immunodeficiency (CVID) (n = 7) (33.33%) and hyper IgM (n = 6) 28.57%. The diagnostic classification was based on clinical and laboratory criteria, not only on immunoglobulin levels. Conclusions: Although no statistically significant differences in immunoglobulin levels were found between groups, the high percentage of patients with profiles suggestive of PID reinforces the importance of performing complete immunologic evaluations in pediatric patients with recurrent infections. Diagnostic confirmation requires clinical correlation and, in some cases, additional studies, so it is recommended to strengthen immunologic evaluation protocols in our context.

Subject Areas

Biochemistry, Immunology, Infectious Diseases, Microbiology, Pediatrics

Keywords

Bacterial Infections, Immunoglobulins, Pediatric Patients, Immunodeficiencies, Inborn Errors in Immunity

1. Introduction

Immunity is a fundamental aspect of human biology, defined as the body's ability to resist disease caused by infection. The body's defense mechanisms fall into two main categories: innate immunity and adaptive immunity. Innate immunity provides initial protection against pathogens, toxins and foreign molecules, while adaptive immunity, although slower to develop, offers a more specific and long-lasting defense [1]. The latter is subdivided into cell-mediated immunity, mediated by T lymphocytes, and humoral immunity, mediated by B lymphocytes, which produce specific antibodies against antigens present in pathogens. The antibodies, once generated, are secreted into the circulation and mucous membranes, where they play a crucial role in the neutralization and elimination of microbes and toxins [2].

Immunoglobulins, such as IgG, IgA and IgM, are essential to the immune response, as they help eliminate pathogens through various functions, such as

neutralization and opsonization. Neutralization prevents pathogens or their toxins from interacting with host cells, while opsonization facilitates the ingestion of pathogens by phagocytes [3]. The causative agents of infections are diverse, including prions, viruses, bacteria, fungi, protozoa and parasites, which can be classified as overt or opportunistic pathogens. Bacterial infections usually follow a three-stage pattern: adherence, resistance to the immune response and tissue attack, facilitated by virulence factors [4].

Recurrent infections, which require differential diagnoses, are characterized by high frequency, severity and persistence. Criteria for identifying recurrent infections include the occurrence of multiple severe infections in one year and the need for prolonged treatment [5]. In this context, primary immunodeficiencies (PIDs) represent a heterogeneous group of genetic diseases that affect the immune response and increase the risk of severe infections. These can be classified into different types, with humoral PIDs being the most frequent and best studied [6]. However, although humoral immunity is the most commonly affected and detected in patients with recurrent infections, other immune defects, such as combined immunodeficiencies or those related to the cellular response, also contribute significantly to susceptibility to infections and may go unnoticed in early stages or with atypical presentations.

Despite the importance of assessing complete immune function, most diagnostic studies in the context of recurrent infections in pediatrics focus on the measurement of serum immunoglobulins (IgG, IgA and IgM) to detect defects in humoral immunity [7]. However, there is a gap in knowledge regarding the actual prevalence of immune deficiencies in different populations, especially in regions where access to specialized diagnostics may be limited. In addition, early and accurate identification of humoral immunodeficiencies can facilitate interventions that prevent severe complications and improve patients' quality of life [8] [9].

The present work, therefore, seeks to fill an important gap in regional knowledge on the prevalence of humoral immunity deficiencies in children with recurrent infections and to highlight the relevance of the laboratory as a diagnostic tool in the timely detection of primary immunodeficiencies, especially those affecting the humoral response [10] [11].

2. Materials and Methods

2.1. Patients and Study Design

The study is descriptive, prospective and cross-sectional, focused on pediatric patients attended in the Pediatric II Service of the University Hospital Complex "Ruíz y Páez" in Ciudad Bolívar, between April and July 2024.

2.2. Ethical Aspects and Informed Consent

The study was conducted in accordance with the ethical principles for medical research on human beings of the Declaration of the Declaration of Helsinki [12], with the corresponding signed informed consent of all patients.

2.3. Instruments

Patients were classified as having PID if they met at least one of the Jeffrey Modell Foundation criteria, which include a clinical history of severe recurrent infections and/or characteristic laboratory findings, mainly low and high immunoglobulin levels. Diagnostic assignment was primarily clinical, supported by immunoglobulin levels. When clinical and laboratory evidence was concordant, the diagnosis was confirmed. Other tests such as vaccine response and/or analysis of lymphocyte subpopulations were not performed because this represents the main limitations of the study, which allows the opening of future research to answer these questions.

2.4. Procedure

The procedure began with obtaining ethical permissions and communication with the Pediatrics Service II staff. Parents were informed about the research and informed consent was obtained. Then, blood samples were collected by venous puncture, following a strict aseptic protocol. Patient data were identified and the child was positioned comfortably. After puncture, the sample was aspirated and transferred to tubes without additive. The samples were centrifuged to obtain serum, which was properly stored to avoid inactivation of the antibodies. The blood samples were processed in a private laboratory in Ciudad Bolivar with IgA, IgM and IgG reagents from ELITech Clinical Systems [13]-[15], guaranteeing the quality and precision of the results. Finally, quality control tests were performed to ensure the reliability of the analytical results.

2.5. Statistical Analysis

The results were presented using frequency distribution tables and percentages. The findings were analyzed in terms of qualitative and quantitative variables, using percentages as the main measure. Descriptive and inferential statistics were applied according to the requirements of the study objectives, using SPSSv26 and "R" version 4.3.1 software.

The results of the variables were presented through simple frequency distribution tables with one entry and contingency tables, using absolute values. These tables were prepared in duplicate with the Microsoft Excel® program. For the comparison of variables, Fisher's exact test (bilateral) was applied, considering as statistically significant those results with a confidence margin greater than 95% or a p-value of less than 0.05.

3. Results

3.1. Recurrent Infections in Pediatric Patients

In pediatric patients, recurrent infections were identified, and it was observed that skin abscesses and pneumonia (n = 6) were the most frequent with 20.00% each; followed by oral aphthous ulcers (n = 5) which represented 16.68%; osteomyelitis and cellulitis (n = 4) with 13.33% each. Finally, with lower percentages, otitis (n =

3) was described with 10.00%; and bacteremia and sepsis (n = 1) which constituted 3.33% each (See Table 1).

Table 1. Recurrent infections in patients of the Pediatrics II service, University Hospital Complex "Ruíz y Páez", Ciudad Bolivar, Bolivar State, April-July 2024.

Infections	n	%
Cutaneous abscesses	6	20
Pneumonía	6	20
Oral thrush	5	16.68
Osteomyelitis	4	13.33
Cellulitis	4	13.33
Otitis	3	10
Bacteriemia	1	3.33
Sepsis	1	3.33
Total	**30**	**100**

Source: Investigator's data, April 2025.

3.2. Gender and Age Group of Pediatric Patients with Recurrent Infections

When classifying pediatric patients according to gender and age, it was evident that female patients predominated (n = 18) with 60.00%; and those in the 3 - 5 years' age group (n = 14) accounted for 46.67% (See Table 2).

Table 2. Gender and age group of pediatric patients with recurrent infections, Pediatrics Service II, University Hospital Complex "Ruíz y Páez", Ciudad Bolivar, Bolivar State, April-July 2024.

Characteristic	n	%
Gender		
Female	18	60
Male	12	40
Age (*years*)		
<1 - 2	6	20
3-May	14	46.67
6-Aug	4	13.33
9-Nov	6	20
Subtotals	**30**	**100**

Source: Researcher's data, April 2025.

3.3. IgA, IgM and IgG Immunoglobulins in Pediatric Patients with Recurrent Infections

In the quantification of immunoglobulins, IgA levels were normal (n = 16) with 53.33% and low (n = 14) representing 46.67%. In IgM normal levels (n = 19) with

63.33%; low (n = 5) in 16.67% of the patients and high (n = 5) in 20.00% of the population studied. Finally, normal IgG levels (n = 23) in 76.67% and low IgG levels (n = 7) represented 23.33% (See Table 3).

Table 3. IgA, IgM and IgG immunoglobulins in pediatric patients with recurrent infections, Pediatrics Service II, University Hospital Complex "Ruíz y Páez", Ciudad Bolivar, Bolivar State, April-July 2024.

	IgA		IgM		IgG	
Level	**n**	**%**	**n**	**%**	**n**	**%**
Normal	16	53.33	19	63.33	23	76.67
Low	14	46.67	5	16.67	7	23.33
High	-	-	6	20	-	-
Totals	**30**	**100**	**30**	**100**	**30**	**100**

Source: Researcher's data, April 2025.

3.4. Relation of Recurrent Infections with IgA, IgM and IgG Levels in Pediatric Patients

When relating recurrent infections in pediatric patients, it is evident that with respect to IgA levels, low levels were found in pneumonia and otitis (n = 3) representing 10.00% each. Regarding IgM levels, high values were observed in patients with cutaneous abscesses (n = 2) with 6.67%; and low values in patients with pneumonia and cellulitis (n = 2) that constituted 6.67% each. Likewise, in relation to IgG levels, low levels were observed in pneumonia and cellulitis (n = 2) with 6.67% each. No statistically significant differences ($p > 0.05$) were observed between the variables under study (See Table 4).

Table 4. Recurrent infections according to IgA, IgM and IgG levels in pediatric patients, Pediatrics Service II, University Hospital Complex "Ruíz y Páez", Ciudad Bolivar, Bolivar State, April-July 2024.

	IgA				IgM						IgG			
	Normal		Low		Normal		High		Low		Normal		Low	
Infections	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Cutaneous abscesses	4	13.33	2	6.67	3	10	2	6.67	1	3.33	5	16.67	1	3.33
Pneumonía	3	10	3	10	3	10	1	3.33	2	6.67	4	13.33	2	6.67
Oral thrush	3	10	2	6.67	4	13.34	1	3.34	-	-	4	13.34	1	3.33
Osteomyelitis	4	13.33	-	-	3	10	1	3.33	-	-	3	10	1	3.33
Cellulitis	2	6.67	2	6.67	1	3.33	1	3.33	2	6.67	2	6.67	2	6.67
Otitis	-	-	3	10	3	10	-	-	-	-	3	10	-	-
Bacteremia	-	-	1	3.33	1	3.33	-	-	-	-	1	3.33	-	-
Sepsis	-	-	1	3.33	1	3.33	-	-	-	-	1	3.33	-	-
Total	**16**	**53.33**	**14**	**46.67**	**19**	**63.33**	**6**	**20**	**5**	**16.67**	**23**	**76.67**	**7**	**23.33**

Fisher's exact test (with IgA) = 0.2019; (with IgM) = 0.8666; (with IgG) = 0.9213; ($p > 0.05$); Not significant. Source: Investigator's data, April 2025.

3.5. Primary Immunodeficiencies in Pediatric Patients with Recurrent Infections

Primary immunodeficiencies were identified in pediatric patients and selective IgA deficiency (n = 8) was observed with 38.10%; common variable immunodeficiency (n = 7) in 33.33% of cases; and finally, Hyper IgM (n = 6) which represented 28.57% (See Table 5).

Table 5. Primary immunodeficiencies in pediatric patients with recurrent infections, Pediatrics Service II, University Hospital Complex "Ruíz y Páez", Ciudad Bolivar, Bolivar State, April-July 2024.

Primary immunodeficiency	n	%
Selective IgA deficiency	8	38.1
Common variable immunodeficiency	7	33.33
Hyper IgM	6	28.57
Total	**21**	**100**

Source: Investigator's data, April 2025.

4. Discussion

Humoral immunity plays a crucial role in the body's defense against infections, tumor cells and allergens, especially in the pediatric population, which is the most vulnerable due to the continuous development of the immune system in the early stages of life, which can be interrupted by genetic conditions that trigger errors in its functioning.

When pointing out recurrent infections in pediatric patients, it was evidenced that cutaneous abscesses and pneumonia were the most frequent with 20.00% each; followed by oral aphthous ulcers 16.68%, osteomyelitis and cellulitis with 13.33% and to a lesser extent otitis 10.00%, bacteremia and sepsis 3.33% each. These findings are similar to those obtained by Yousefzadegan *et al.* [16] in which they selected 100 patients under 14 years of age, referred to different services of the Children's Medical Center of Tehran, Iran, during one year, in which they pointed out that the most frequent infections were lower respiratory tract infections 31% and upper respiratory tract infections 30.00%, followed by severe systemic infections 13.00%, gastrointestinal infections 11.00%, soft tissue infections or abscesses 1% and skin infections 4.00%.

When classifying the study population according to gender and age, there was a predominance of female patients 60.00% versus male patients 40.00%, as well as the age group of 3 to 5 years 46.67%. These findings differ with the study by Monet *et al.*, 2021 [9] "Serum immunoglobulin levels in pediatric patients with recurrent respiratory infections", where 67.87% of patients were male and 21.43% were less than one-year-old. Differences in gender distribution in recurrent infections may be influenced by several factors, such as exposure to pathogens, maturation of the immune system, and genetic factors associated with gender.

Regarding the quantification of immunoglobulins, 53.33% of the patients had normal IgA levels, while 46.67% had low levels. Regarding IgM, 63.33% showed normal levels, 20% had high levels, suggesting a possible acute response to recent infections, and 16.67% had low levels, indicating immune dysfunction. As for IgG, 76.67% of the patients had normal levels, while 23.33% showed low levels, which could increase the risk of severe or persistent infections due to lack of immunologic memory.

These findings are consistent with the study by Ferreira *et al.* [17] "Serum immunoglobulin levels in children with recurrent infections", in which 12% of patients were found to have low levels of IgA and IgG, and 64.7% had high levels of IgM. Although children with normal IgA, IgM and IgG levels were observed in the population studied, there is also a significant proportion of patients with low IgA and IgG levels, as well as a notable number of patients with elevated IgM levels. This suggests that, although many children have normal levels of these immunoglobulins, a portion of the population studied may be at risk for recurrent infections. The similarity in the results between the two studies reinforces the idea that alterations in immunoglobulin levels may be an important marker for identifying children susceptible to these infections.

When relating recurrent infections in pediatric patients with immunoglobulin levels, the following findings were found: in the case of IgA, low levels were observed in patients with pneumonia and otitis, each representing 10.00%. As for IgM, high values were recorded in patients with skin abscesses at 6.67%, and low levels were recorded in those with pneumonia and cellulitis, which also constituted 6.67% each. Regarding IgG, low levels were identified in patients with pneumonia and cellulitis, with 6.67% each. However, no statistically significant differences ($p > 0.05$) were found between the variables studied.

These findings are in agreement with the study by Caballero *et al.*, [18] entitled "Antibody deficiencies in children and adolescents with recurrent and/or severe infections". In which they reported that, of 7 patients with recurrent pneumonia, 71.42% presented low levels of IgA, while 28.57% showed normal levels. In relation to IgM, elevated levels were observed in one patient with recurrent adenopathy and pneumonia 50.00% and in another with recurrent pneumonia 14.29%. Three patients with pneumonia presented normal values 42.86% and two showed low levels 28.57%. As for IgG, all patients with recurrent pneumonia and adenopathies showed low values 100.00%, while two patients with allergy showed normal values 66.66%.

The recognition of primary immunodeficiencies in pediatric patients is essential to provide adequate care. Jeffrey Modell's criteria were used, which include alarm signs such as frequency and severity of recurrent infections, family history of immunodeficiencies and aspects related to the child's growth. It was found that 38.10% of the patients had selective IgA deficiency, the most common form of primary immunodeficiency, which increases susceptibility to respiratory and gastrointestinal tract infections. The 33.33% had common variable immunodeficiency, which translates into decreased antibodies and increased vulnerability to

infections. Hyper IgM, observed in 28.57% of the cases, is characterized by high levels of IgM and low levels of IgG and IgA, compromising the immune system.

The prevalence of primary immunodeficiencies (PID) in our study, in particular selective IgA deficiency, presents a frequency of 38.10%, a figure slightly higher than that estimated in international studies, where the prevalence of IgA deficiency in pediatric populations varies between 1% and 5% in different regions [16] [17]. Regionally, specific data for our population are still scarce, but existing studies in Latin American countries report similar or slightly higher prevalences [9]. The high prevalence observed could reflect genetic, environmental or exposure to particular infectious agents in the population studied, although further research is required to confirm these hypotheses.

The present study has several limitations that should be considered when interpreting the results. First, the sample size is relatively small, which limits the generalizability of the findings and reduces the statistical power to detect significant differences in some comparisons, such as those related to recurrent infections and immunoglobulin levels ($p > 0.05$).

In addition, the absence of confirmatory diagnostic tests, such as specific genetic studies or immunological functional tests, limits the accuracy in classifying the types of PID and may lead to an underestimation or overestimation of its prevalence. The lack of longitudinal follow-up also makes it impossible to determine the clinical evolution of patients and the response to therapeutic interventions.

In a study by Wu *et al.* [19] "Primary immunodeficiency disease: a retrospective study of 112 Chinese children in a single tertiary care center" in which 12 children with (PID) were diagnosed and classified according to the 2017 criteria presented by the International Union of Immunology Societies (IUIC) in a single tertiary care center between January 2013 and November 2018. The most frequently diagnosed (PID) was severe combined immunodeficiency (SCID) 28.6% and hyper IgM (HIGM) syndrome 24.1%, followed by predominantly antibody deficiencies 17.8%.

When contrasting the results obtained with those of the study by Wu *et al.* [19] it was observed that while selective IgA deficiency and CVID predominated in the study by Wu, a higher frequency of severe combined immunodeficiency CGID and hyper IgM syndrome was reported in the study by Wu. Importantly, despite the differences in prevalences, hyper IgM syndrome was identified in both studies, although with different relative frequencies, suggesting its clinical relevance in diverse populations.

The findings of the present study regarding the most frequent possible (PIDs) in the studied population have relevant clinical implications. The high prevalence of selective IgA deficiency suggests the need for its consideration in pediatric patients with recurrent infections, regardless of the initial severity of symptoms. Likewise, the identification of a significant proportion of cases of CVID and hyper IgM emphasizes the relevance of a thorough immunologic evaluation in suspected cases of PID, aimed at an accurate classification and an individualized therapeutic approach.

5. Conclusion

The study identifies pneumonia and skin abscesses as the most common infections in the pediatric population analyzed, suggesting their high prevalence. Factors such as exposure to pathogens and immunological susceptibility of children could influence this trend. Although most patients have normal immunoglobulin levels, some show deficiencies that make them vulnerable to recurrent infections. The importance of diagnosing conditions such as selective IgA deficiency and common variable immunodeficiency is highlighted. The findings suggest the need to thoroughly evaluate immune function in children with recurrent infections to improve their treatment and quality of life.

Recommendations

It is recommended to promote studies on the prevalence of recurrent infections in pediatric populations at regional and national levels. It is crucial to develop awareness campaigns, focusing on children aged 3 to 5 years, to promote seeking medical attention for persistent symptoms. In addition, clinical laboratories should be provided with reagents to evaluate serum immunoglobulins and their relationship with susceptibility to infections. Adopting warning signs from the Jeffrey Modell Foundation will facilitate the identification of primary immunodeficiencies. It is also vital to train health professionals in the management of these infections and to follow up patients with normal immunoglobulins.

Acknowledgements

The authors would like to thank the private institution where the samples were processed, as well as the pediatric service II of the Complejo Hospitalario Universitario Ruiz y Paez.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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