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ORIGINAL ARTICLE

Pulmonary complications in pediatric patients with primary immunodeficiency (PI)

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Abstract

Introduction: *Primary immunodeficiencies comprise diseases that impair the immune system. Clinical manifestations are characterized by recurrent respiratory infections, which may be complicated by bronchiectasis, peribronchial thickening, abscesses, bullae, and pulmonary fibrosis. The aim of this study was to determine pulmonary complications in pediatric primary immunodeficiency by type.* **Results**. *We included 65 patients, 28 patients with humoral immunodeficiency, four with cellular immunodeficiency, 13 with well-defined syndromes, and 20 with phagocytic defects. Patients with cellular immunodeficiency with symptoms began at an early age, and were diagnosed before one year of age (p = 0.01). Patients with humoral immunodeficiency had more frequent and early respiratory symptoms (p = 0.01). The most common respiratory diseases were acute suppurative otitis media, with sinusitis and pneumonia more common in humoral immunodeficiencies and phagocytic defects. The most common pulmonary complications were bronchiectasis and pulmonary fibrosis interstitial damage, with no statistical difference between primary immunodeficiency types. Pulmonary function tests showed greater impairment in patients with phagocyte defects, but no statistical difference (p = 0.28). The presence of pulmonary complications showed no difference when compared by type of immunodeficiency, agammaglobulinemia only (p = 0.02).* **Conclusions:** *Cell immunodeficiencies are diagnosed as early as the onset of symptoms before the patient is one year old. Humoral immunodeficiencies present maximum upper and lower respiratory infections and increased risk of pulmonary complications, especially agammaglobulinemia.* (Gac Med Mex. 2015;151:145-51)

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Introduction

Prlmary immunodeficiencies (PIDs) are a group of hereditary diseases that comprises alterations in the development of the immune system, its function, or both. Clinical manifestations often occur within the first 5 years of life. Age at diagnosis of immunodeficiencies occurs between one and two years after the onset of symptoms[1-12]. PIDs are characterized for the occurrence of infections caused by capsulated extracellular bacteria and these patients show higher susceptibility to autoimmune, infectious, especially respiratory conditions, which can become complicated with bronchiectasis, peribronchial thickening, mucus plugs formation, pulmonary overdistension, bronchiolitis, alveolitis, consolidation processes or abcesses, bullae, emphysema and fibrotic changes[13-15,26,28,34, 39-41]. The purpose

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Table 1. Clinical characteristics of 65 patients with PID from a tertiary care hospital of Monterrey (Nuevo León)*

	Humoral immunodeficiencies (n = 28)	Cell-mediated immunodeficiencies (n = 4)	Well-defined syndromes (n = 13)	Phagocytic defects (n = 20)	p-value	Total (n = 65)
Sex						
Males	22	2	10	11		45
Females	6	2	3	9	0.83	20
Age at diagnosis (years)	5 (4 months-15 years)	1 (4 months -1 year and 6 months)	2 (10 days -7 years)	3 (10 days -15 years	0.01	
Age at start of symptoms	2 (3 months -15 years)	0.5 (10 days -5 years)	1 (10 days -15 years)	2 (10 days -15 years)	0.05	
Age at first respiratory symptom (years)	0.5 (4 months -3 years)	1 (4 months -1.5 years)	6 (0.01 -6 years)	4 (10 days -10 years)	0.01	

*Values expressed in means (ranges); statistical significance: $p \leq 0.05$.

of this study was to determine the pulmonary complications in pediatric patients according to their PID type.

Material and methods

Medical records of patients diagnosed with PID prior to the age of 16 years and who were controlled at the pediatric immunology outpatient clinic of a tertiary care hospital, Nº 25 UMAE of Monterrey, in the state of Nuevo León, were reviewed.

The following information was collected in a case report form: sex, type of PID, age at the onset of symptoms, age at diagnosis, recurrent infections, respiratory symptoms and pulmonary radiological and functional abnormalities. The patients were divided to be studied according to the type of PID: humoral immunodeficiencies, cell-mediated immunodeficiencies, well-defined syndromes and phagocytic defects. Data was analyzed using descriptive statistics, as well as the chi-square test to determine the odds ratio (OR), with a 95% confidence interval (IC), with statistical significance established at a p-value < 0.05.

Results

Sixty-five patients, diagnosed with PID in a tertiary care hospital of the Mexican Social Security Institute (IMSS – *Instituto Mexicano del Seguro Social*) from Monterrey, Nuevo León, were included, and out of which 45 (69.2%) were males and 20 (30.7%) were females.

The patients were classified into 4 groups according to the type of PID: 28 patients (43%) with humoral immunodeficiencies, 4 (2.6%) with cell-mediated immunodeficiencies, 13 (8.45%) with well-defined syndromes and 20 (30.7%) with phagocytic diseases.

Median age at diagnosis was 5 years (4 months-15 years) for humoral immunodeficiency, 1 year (4 months-1 year and 6 months) for cell-mediated immunodeficiencies, 2 years (10 days-7 years) for well-defined syndromes and 3 years (10 days-15 years) for phagocytic diseases (p = 0.01). Median age at symptoms onset was 2 years (3 months-15 years) for humoral immunodeficiencies, 6 months (10 days-6 months) for cell-mediated immunodeficiencies, the first year of life (10 days-5 years) for well-defined syndromes and 2 years (10 days-1 year and 6 months) for phagocytic diseases (p = 0.05). Median age at onset of the first respiratory symptom in patients with humoral immunodeficiencies was 0.5 years (0.3-3); in the group of cell-mediated immunodeficiencies it occurred at 1 year of age (0.3-1.5); in well-defined syndromes, at 6 years (0.01-6) and in phagocytic diseases, at 5 years of age (0.3-10) (p = 0.01) (Table 1).

There were 4 (0-40) episodes of acute suppurative otitis media (ASOM) among patients with humoral immunodeficiencies; in the group of patientes with cell-mediated immunodeficiencies it did not occur; in those with well-defined syndromes there were 3 (0-11) cases, and in those with phagocytic diseases there were also 3 (0-12) cases (p = 0.47). With regard to sinusitis episodes, in the group of humoral immunodeficiencies there were 4 (0-20) cases, in the group with cell-mediated immunodeficiencies 1 (0-5), in the group with well-defined syndromes 6 (0-15) and in the group with phagocytic defects 3 (0-10) (p = 0.24). In patients with humoral immunodeficiencies, pneumonia

Table 2. Respiratory diseases in 65 patients with PID from a tertiary care hospital in Monterrey (Nuevo León)*

	Humoral immunodeficiencies (n = 28)	Cell-mediated immunodeficiencies (n = 4)	Well-defined syndromes (n = 13)	Phagocytic defects (n = 20)	p-value
ASOM episodes	4 (0-40)	0 (0-5)	3 (0-11)	3 (0-12)	0.47
Sinusitis episodes	4 (0-20)	1 (0-5)	6 (0-15)	3 (0-10)	0.24
Pneumonia episodes	5 (0-30)	4 (0-5)	2 (0-6)	4 (0-30)	0.27
Pleural effusion episodes	1 (0-1)	0 (0)	0	0	–
Bronchitis episodes	2 (0-2)	1 (0-5)	1 (0-5)	0.5 (0-5)	0.67
Pneumothorax episodes	1 (0-2)	1 (0-1)	1 (0-1)	2 (0-2)	–

*Values expressed in means (ranges); statistical significance: $p \leq 0.05$.

occurred in 5 (0-30); in those with cell-mediated immunodeficiencies, in 4 (0-5); in those with well-defined syndromes, in 2 (0-6), and in those with phagocytic diseases, in 4 (0-30) (p = 0.27). Pleural effusion occurred in 1 (0-1) patient with humoral immunodeficiencies; no pleural effussion occurred in patients with cell-mediated immunodeficiencies, well-defined syndromes and phagocytic diseases. Acute bronchitis occurred in 2 (0.2) cases of the group with humoral immunodeficiency, in 1 (0-2) of the cell-mediated immunodeficiencies group, in 1 (0-5) of the well-defined syndromes group and in 0.5 (0-5) of the phagocytic diseases group (p = 0.67). There was pneumothorax in 1 (0-2) patient with humoral immunodeficiencies, in 1 (0-1) with well-defined syndromes and in 2 (0-2) with phagocytic disease (Table 2).

Among the patients with humoral immunodeficiencies, there were 14 (50%) with pulmonary complications, complications that occurred in 3 (75%) patients with cell-mediated immunodeficiencies, in 4 (30%) with well-defined syndromes and in 12 (60%) with phagocytic diseases (p = 0.29). Two cases of pulmonary fibrosis were detected in the group of patients with humoral immunodeficiencies; no cases were detected in the groups with cell-mediated immunodeficiencies and well-defined syndromes and among the patients with phagocytic diseases, one experienced this abnormality (p = 0.52). There was one case of chronic atelectasis in the humoral immunodeficiencies group; no cases were found among the patients with cell-mediated immunodeficiencies, well-defined syndromes and phagocytic diseases (p = 0.72). Bronchiectasis was detected in 5 patients with humoral immunodeficiencies, in 3 with cell-mediated immunodeficiencies, in 2 with well-defined syndromes and in 5 with phagocytic diseases (p = 0.12). With regard to interstitial abnormality, it occurred in 6 patients with humoral immunodeficiencies; no cases were found in the cell-mediated immunodeficiencies group; and there were 2 cases in the well-defined syndromes group and 4 in the phagocytic diseases group (p = 0.28). Pulmonary hypertension did not occur in any patient. PFT abnormalities in patients diagnosed with humoral immunodeficiencies occurred in 12 cases (42%), as well as in 3 (75%) of the patients with cell-mediated immunodeficiencies and in 8 (40%) of those with well-defined syndromes (p = 0.28). Hematopoietic cell transplantantion was performed in 2 patients with cell-mediated immunodeficiencies and in 3 with well-defined syndromes. Twenty-two patients (78%) with humoral immunodeficiencies, 2 (50%) with cell-mediated immunodeficiencies, 11 (84%) with well-defined syndromes and 19 (95%) with phagocytic diseases survived (p = 0.13) (Table 3).

Of the 28 patients with humoral immunodeficiencies, 13 (46%) had agammaglobulinemia; 6 (21.4%), common variable immunodeficiency; 4 (14%), hyperimmunoglobulin M syndrome (Hyper-IgM); 4 (14%), defect in Ig subclasses, and 1 (3.5%), polysaccharide defect. In the cell-mediated immunodeficiencies, severe combined immunodeficiency was diagnosed in 4 patients. Thirteen patients were included in the well-defined syndromes, out of which 6 (46%) had Wiskott-Aldrich syndrome (WAS); 3 (23%), ataxia-telangiectasia; 3 (23%), Di George syndrome, and 1 (15%), chronic mucocutaneous candidiasis. Twenty patients were included in the phagocytic diseases group, out of which 4 (20%) had Chediak-Higashi disease; 3 (15%), chronic granulomatous disease, and 13 (65%), hyperimmunoglobulin E syndrome (Hyper-IgE).Of the patients with humoral immunodeficiency, those with agammaglobulinemia

Table 3. Pulmonary complications in 65 patients with PID from a tertiary care hospital in Monterrey (Nuevo León)*

	Humoral immunodeficiencies (n = 28)	Cell-mediated immunodeficiencies (n = 4)	Well-defined syndromes (n = 13)	Phagocytic defects (n = 20)	p-value
Pulmonary complication	14 (50%)	3 (75%)	4 (30%)	12 (60%)	0.29
Pulmonary fibrosis	2	0	0	1	0.52
Chronic alectasis	1	0	0	0	0.72
Bronchiectasis	5	3	2	5	0.12
Pulmonary hypertension	0	0	0	0	–
Interstitial damage	6	0	2	4	0.28
PFT abnormality	12 (42%)	1 (25%)	4 (30%)	8 (70%)	0.28
BM transplantation	0	2	3	0	–
Deaths	6	2	2	1	0.13

*Values expressed in means (ranges); statistical significance: $p \leq 0.05$.

showed a higher frequency of pulmonary complications when compared with other immunodeficiencies (OR: 1.85; 95% CI: 1.1-9.3; p = 0.02).

In cell-mediated immunodeficiencies, severe combined immunodeficiency produced pulmonary complications in 3 patients (OR: 3; 95% CI: 0.66-17.95; p = 0.22). In the well-defined syndromes group, there were 4 patients with pulmonary complications and 9 with no complications (OR. 0.5; 95% CI: 0.17-1.7; p = 0.283). Twelve of the patients with phagocytic diseases experienced pulmonary complications, with the most common being chronic granulomatous disease and Hyper-IgE syndrome (OR: 2.56; 95% CI: 0.41-17.23; p = 0.24) (Table 4).

Discussion

PIDs are a group of conditions characterized by alterations in cell-mediated (T-lymphocyte) and humoral (B-lymphocyte)-specific immunity or in the defense mechanisms of the host (phagocytic cells, cytokines, proteins of the complement, among others). These disorders in the immune system result in an increased susceptibility to infections and to the probable development of autoimmune conditions[1-4].

With regard to their distribution by sex, almost all records show a large male predominance (60-80%), with a 5:1 ratio over females[16,17,19]. In this study, the male:female ratio was 2:1.

Clinical manifestations occur commonly within the first 5 years of life; however, they can occur at any age, including adult age[17,19]. In this study, the onset of symptoms occurred at early ages and before one year of age in the case of cell-mediated immunodeficiencies; with the other immunodeficiencies, it occurred at later stages of chilhood, but most of them before 5 years of age, just as reported in literature. Age at immunodeficiencies diagnosis is 1-2 years on average and 2 years after the onset of symptoms; however, cell-mediated immunodeficiencies are diagnosed earlier due to the severity of stmptoms, which may start as early as the first days of life with life-threatening infections, whereas humoral immunodeficiencies and phagocytic defects have a variable age of onset, which can range from early childhood to adult life. Age at PID diagnosis is variable; other studies report an average age at diagnosis between 4.3 and 6 years[39,40], reflecting the lack of adequate data the medical area has on PID. In this study, average age at PID diagnosis was earlier: 2.7 years.

PID clinical manifestations can be very varied, depending on the immune defect; there is failure to thrive due to repetition infections suffered during the first years of life; defects involving any alteration in the B-lymphocyte function result in recurrent pulmonary infections, often associated with bacterial septicemia[1-4,21]. In humoral and cell-mediated immunodeficiencies, respiratory symptoms appear during the first year of life, and in well-defined syndromes and phagocytic defects, later than this age.

Upper respiratory tract infections occurred in more than 80% of the patients with PID, including ASOM and

Table 4. Pulmonary complications according to PID type in 65 patients from a tertiary care hospital in Monterrey (Nuevo León)*

Type of immunodeficiency	With pulmonary complications	Without pulmonary complications	p-value	OR (95% CI)
Humoral (n = 28)	14	14	0.02	1.85 (1.1-9.3)
Agammaglobulinemia (n = 13)	10	3		
Common variable immunodeficiency (n = 6)	3	3		
Hyper-IgM syndrome (n = 4)	1	3		
Defect in Ig subclasses (n = 4)	0	4		
Polysaccharide defect (n = 1)	0	1		
Cell-mediated (n = 4)				
Severe combined immunodeficiency	3	1	0.22	3 (0.66-17.95)
Well-defined syndromes (n = 13)	4	9	0.28	(0.17-1.77)
WAS (n = 6)	2	4		–
Ataxia-telangiectasia (n = 3)	1	2		
Di George syndrome (n = 3)	0	3		
Mucocutaneous candidiasis (n = 1)	1	0		
Phagocytic (n = 20)	12	8	0.24	(0.41-17.0)
Chediak-Higashi (n = 4)	1	3		
Chronic granulomatous disease (n = 3)	3	0		
Hyper-IgE syndrome (n = 13)	8	5		
Total	33	32		

*Values expressed as means (ranges).

sinusitis; lower respiratory tract infections include bronchitis and pneumonia, as well as their complications. In previous studies, patients with humoral immunodeficiencies, especially those diagnosed with agammaglobulinemia and common variable inmunodeficiency, are reported to experience chronic sinusitis in more than half of the cases[22-25]. Defects involving any disturbance in B-cell functions result in recurrent pulmonary infections that often and, depending on the humoral response involvement, can result in sepsis[16]. Other PID complication is chronic sinusitis, which in some studies can be as high as 70.6%[41]. Mogica Martínez et al. reported that 19 subjects (79%) had this condition, in particular maxillary sinusitis[39]. Acute bronchitis and pneumonia episodes, which are severe infectious conditions, affect patients with PID, especially those with the humoral type[24,25]. In this study, ASOM and sinusitis were predominant in patients with humoral immunodeficiencies and well-defined syndromes, while pneumonia was more frequent in humoral and cell-mediated immunodeficiencies, as well as in phagocytic diseases. Patients experiencing more complications such as pleural effusion and pneumothorax were those from the groups of humoral immunodeficiency and phagocytic defects, but the difference was not statistically significant. Patients who develop a pulmonary complication are likely to experience fibrosis if they have high levels of transforming growth factor b, which has been proven in epithelial cells, upper respiratory tract end macrophages and in alveoli. This phenomenon precedes visible fibrotic alterations and pulmonary function and tissue remodelling abnormalities[38]. Repeated infections can turn into pulmonary complications, such as bronchiectasis, peribronchial cuffing, mucus plugs formation, pulmonary overdistension, bronchiolitis, alveolitis, consolidation processes or abcesses, bullae, emphysema and fibrotic changes. In a report on 19 patients diagnosed with humoral immunodeficiencies assessed with thoracic high-resolution computed tomography, bronchiectasis, mucus plugs, interstitial alterations, peribronchial cuffing, atelectasis and consolidation areas were found to be the main pulmonary complications[27]. Other studies report an important pulmonary involvement in patients with agammaglobulinemia: bronchial thickening (30%), bronchiectasis (12%), interstitial infiltrate (6%), atelectasis (2%), pleural thickening (1%) and bullae (1%)[27-29]. Some authors have reported bronchiectasis and pulmonary abscesses in 26% of the cases[36,37]. Mogica Martínez et al. reported that chronic pneumopathies were detected in two thirds of 24 patients with different types of PID, with brinchiectasis being the most common complication (75%)[39]. In the present study, the most common pulmonary complications were bronchiectasis,

followed by interstitial damage and pulmonary fibrosis, which were more frequent in patients with humoral immunodeficiency and in those with phagocytic defects.

PFT abnormalities have not been thoroughly studied in patients with PID. Rusconi et al. assessed a group of patients with recurrent episodes of agammaglobulinemia, common variable immunodeficiency, immunoglobulin A (IgA) deficit and severe combined immunodeficiency; of all 21 reported patients, 17 had a normal spirometry, and only in 4 it was abnormal, with a mild obstructive-type pattern[34]. Other study has reported PFT abnormalities only in 33.3% of the cases, with predominance of the moderate-to-severe degree obstructive pattern[37]. In this study, PFT abnormalities were more frequent in phagocytic diseases and humoral immunodeficiencies, but with no statistically significant difference. Of note, it is important for antiinflammatory and bronchodilator treatment to be implemented as needed.

In the humoral immunodeficiencies group, agammaglobulinemia had a higher incidence of pulmonary complications, with a statistically significant difference, compared with other humoral-type conditions, as well as with the rest of immunodeficiencies.

Agammaglobulinemia had pulmonary complications in up to 71% of cases in a report by Rusconi et al. and Lederman et al.[34,35]. In the present study, it occurred in 66% of the patients with pulmonary complications. Pulmonary complications have been reported in 85% of variable common immunodeficiency cases[33], in contrast with 50% in this work. Patients with immunoglobulin G (IgG) subclasses defect experience recurrent sinopulmonary infections, especially those with the IgG2 type, due to a lack of anti-polysaccharide antibodies production and recurrent infections by capsulated bacteria[29]; in this study, there was only a patient with no pulmonary complications. On the other hand, in the Hyper-IgM syndrome, pulmonary presentation reflects a loss of resistance to capsulated bacteria, characterized by recurrent sinobronchial infections. In a report with 79 patients, the onset of respiratory symptoms before the age of 4 years occurred in 90% of the cases[30,31]. Buckley reported that 15% of patients with combined immunodeficiency experienced pulmonary complications[32]; in this work, they occurred in 75% of the patients. In the phagocytic diseases group, pulmonary manifestations, either viral and/or bacterial, are recurrent, are caused mainly by *Staphilococcus aureus* and later are complicated with chronic pneumonia[30-30]; in this work, 40% of the patients had pulmonary complications.

As for the prevalence of PIDs, there are different reports, as the one published by the Latin American Group for Primary Immunodeficiency Diseases (LAGID) in 1988, according to which, in 1,428 patients, PIDs associated with antibody defects were the most common (58%), followed by well-defined syndromes (18%), phagocytic disorders (9%), abnormalities associated with defects in granulocytes (8%), severe combined immunodeficiency (5%) and complement deficiencies (2%)[20]. Humoral immunodeficiencies were the most predominant group in the study population, and agammaglobulinemia, the most common condition in this group; for phagocytic defects, Hyper-IgE syndrome was the most reported condition, consistent with the literature[19,20]. In this study, in the groups of cell-mediated immunodeficiencies and antibodies associated with other major defects (well-defined syndromes), WAS was the most frequent diagnosis, in contrast with a report from Colombia, where chronic mucocuteneous candidiasis was the most frequent disease in the group[19,20].

PIDs comprise a group of diseases characterized by defects in the immune complex that should be considered in patients that experience recurrent infections, since timely diagnosis and treatment can prevent complications associated with these conditions, mainly those of respiratory origin. The main respiratory complications found in this study were bronchiestasis, interstitial damage and pulmonary fibrosis, which, together with the underlying immunodeficiency, favor lower respiratory tract infections recurrence due to an accumulation of secretions. Humoral immunodeficiencies such as agammaglobulinemia are the conditions with most pulmonary complications, followed by chronic granulomatous disease and severe combined immunodeficiency. These complications can affect the quality of life of children with these immune diseases and put their lives at risk, which is why early detection of susceptible patients and offering an adequate treatment is necessary.

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