

Sinopulmonary Complications in Subjects With Primary Immunodeficiency

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BACKGROUND: The aim of this work was to describe the frequency and spectrum of sinopulmonary complications among subjects with primary immunodeficiency disorders. **METHODS:** The subjects included all patients with primary immunodeficiency who were registered prospectively between January 2004 and December 2013 in the Kuwait National Primary Immunodeficiency Disorders Registry. **RESULTS:** A total of 202 subjects were registered during the study period. Subjects with combined immunodeficiencies were the most prevalent (65 subjects, 32.1%), followed by well-defined syndromes with immunodeficiency (45 subjects, 22.2%) and predominantly antibody deficiencies (35 subjects, 17.3%). A total of 295 sinopulmonary manifestations were observed in 127 subjects (63%); 157 manifestations (53.2%) were observed among the presenting symptoms, and 138 manifestations (46.8%) occurred after establishment of the primary immunodeficiency disorder diagnosis. Sinopulmonary manifestations were more common in subjects with predominantly antibody deficiencies (2.3 manifestations/subject), followed by subjects with combined immunodeficiencies (1.75 manifestations/subject). Pneumonia was the most common manifestation (108 episodes affecting 80 subjects), followed by otitis media (81 episodes affecting 59 subjects), bronchiectasis in 28 subjects (13.8%), and asthma in 22 subjects (11%). Microbial organisms were isolated during 46 episodes of pneumonia (42.5%) (cytomegalovirus and *Pneumocystis jirovecii* were the most common). There were 57 deaths (28%) during the study period. Twenty-four deaths (42%) were due to pulmonary complications as follows: pneumonia (16 subjects, 8%), pulmonary hemorrhage (6 subjects, 3%), and aspiration pneumonia (2 subjects, 1%). **CONCLUSIONS:** Sinopulmonary complications are common in subjects with primary immunodeficiency. They can be serious and continue to occur even after proper treatment is initiated. The pulmonologist should play an important role in the management of subjects with primary immunodeficiency disorder. *Key words:* primary immunodeficiency; pneumonia; bronchiectasis; asthma; complications. [Respir Care 0;0(0):1-•. © 0 Daedalus Enterprises]

Introduction

Primary immunodeficiency disorders are a heterogeneous group of genetic defects in the immune system.¹⁻⁴

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Patients with primary immunodeficiency disorders are more likely to experience recurrent, serious, and unusual infections and have a tendency to develop a wide range of complications.⁵⁻⁷ The true incidence and prevalence of primary immunodeficiency disorders are not known. However, it is now clear that primary immunodeficiency disorders are not as rare as originally assumed several decades ago. The upper estimates suggest that 6 million people

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worldwide may be living with a primary immunodeficiency disorder.⁸ Despite the increasing numbers of primary immunodeficiency disorders diagnosed in the last decade⁹ and a better understanding of immune system functions, many physicians lack knowledge regarding these disorders and do not often consider the possibility of immunodeficiency early enough in the differential diagnosis,^{10,11} resulting in a significant delay in diagnosis and an increased morbidity and mortality.¹²⁻¹⁸

Primary immunodeficiency disorder in Kuwait, a small country located in the Arabian Peninsula, is relatively common with a prevalence of 11.98 in 100,000 children, an incidence of 10.06 in 100,000 children, and an estimated occurrence of 1 in 1,000 live births.¹² This is much higher than the reported prevalence in populations from other ethnicities or geographical regions (eg, 4.4 in 100,000 in France,¹⁹ 5.6 in 100,000 in Australia,²⁰ 1.51 in 10,000 in Germany,²¹ and 2.3 in 100,000 in Japan²²). The high prevalence of primary immunodeficiency disorder in Kuwait is probably caused by the high rate of consanguineous marriages among our population.²³ The aim of this study was to describe the frequency and spectrum of sinopulmonary complications among subjects with primary immunodeficiency disorders registered in the Kuwait National Primary Immunodeficiency Disorders Registry.

Methods

Subjects With Primary Immunodeficiency Disorders

This longitudinal, prospective clinical study was conducted between January 2004 and December 2013 and included all of the patients registered in the Kuwait National Primary Immunodeficiency Registry, which was approved by the Research and Ethics Committee of the Ministry of Health in Kuwait. The subjects were classified according to both clinical and laboratory criteria for primary immunodeficiency disorders reported in 2011 by the International Union of Immunological Societies Primary Immunodeficiency Diseases Committee.²⁴ The possibility of secondary immunodeficiencies (drug-induced, HIV-induced, and immunodeficiency associated with metabolic disorders, among others) was eliminated by obtaining a detailed history and by performing the appropriate testing when these disorders were suspected. The immunological tests performed for our subjects were done using standard techniques and included complete blood count with peripheral blood smear evaluation, serum immunoglobulins, antibody response to previous vaccines, lymphocyte phenotype (T, B, and NK cells) by flow cytometry, lymphocyte stimulation test, autoantibodies, nitro blue tetrazolium dye test, and complement hemolytic activity (CH50) with specific complement component when needed.

QUICK LOOK

Current knowledge

Patients with primary immunodeficiency are more likely to experience a wide range of complications. Unfortunately, many physicians lack knowledge regarding primary immunodeficiency and do not often consider the possibility of immunodeficiency early enough in the differential diagnosis, resulting in a significant delay in diagnosis and an increased morbidity and mortality.

What this paper contributes to our knowledge

Sinopulmonary complications are common in subjects with primary immunodeficiency. They can be serious and continue to occur even after proper treatment is initiated.

Results

A total of 202 subjects were registered during the study period. Combined immunodeficiencies were the most prevalent (65 subjects, 32.1%), followed by well-defined syndromes with immunodeficiency (45 subjects, 22.2%); predominantly antibody deficiencies (35 subjects, 17.3%); diseases of immune dysregulation (30 subjects, 15%); congenital defects of phagocyte number, function, or both (14 subjects, 7%); complement deficiencies (9 subjects, 4.4%); and autoinflammatory disorders (4 subjects, 2%). One hundred eight subjects (53.4%) were treated with intravenous immunoglobulins, 106 (52.5%) were treated with prophylaxis antimicrobial agents, and 49 (24%) received hematopoietic stem cell transplantation.

A total of 295 sinopulmonary manifestations were observed in 127 subjects (63%). One hundred fifty-seven (53.2%) of the manifestations were among the presenting symptoms, and 138 (46.8%) occurred after establishment of the primary immunodeficiency disorder diagnosis. Table 1 shows the frequency of sinopulmonary manifestations according to each primary immunodeficiency disorder category. These manifestations were more common in subjects with predominantly antibody deficiencies (2.3 manifestations/subject), followed by those with combined immunodeficiencies (1.75 manifestations/subject). Pneumonia was the most common manifestation (108 episodes affecting 80 subjects), followed by otitis media (81 episodes affecting 59 subjects), bronchiectasis affecting 28 subjects (13.8%), and asthma affecting 22 subjects (11%) (Table 2). Five subjects (2.5%) (4 with signal transducer and activator of transcription 3 deficiency and one with severe combined immunodeficiency) had pneumonia that was complicated by pneumatocele. Microbial organisms

Table 1. Subjects' Characteristics and Frequency of Sinopulmonary Manifestations According to Each Primary Immunodeficiency Category

PID Category	n (%), Males/Females	Mean Onset Age, mo	Mean Diagnosis Age, mo	IVIG, n (%)	HSCT, n (%)	No. of Sinopulmonary Manifestations (total 295)	No. of Sinopulmonary Manifestations/ Subject
Combined immunodeficiencies	65 (32.1%), 35/30	5.65	17.98	59 (91%)	35 (54%)	114	1.75
Well-defined syndromes with immunodeficiency*	45 (22.2%), 24/21	5.69	30.80	5 (11%)	2 (4.5%)	50	1.1
Predominantly antibody deficiencies	35 (17.3%), 24/11	83.17	130.77	22 (63%)	0	80	2.3
Diseases of immune dysregulation	30 (15%), 16/14	18.33	38.60	11 (36%)	9 (30%)	29	0.9
Congenital defects of phagocyte number, function or both	14 (7%), 6/8	5.00	16.36	4 (28.5%)	3 (21%)	10	0.71
Autoinflammatory disorders†	4 (2%), 4/0	0.25	30.5	0	0	0	0
Complement deficiencies	9 (4.4%), 2/7	42.78	158.00	0	0	12	1.3

* Wischott-Aldrich syndrome, DiGeorge syndrome, STAT3 deficiency, ataxia-telangiectasia, and hepatic veno-occlusive disease with immunodeficiency.

† interleukin-10 deficiency.

PID = primary immunodeficiency disorder

IVIG = intravenous immunoglobulins

HSCT = hematopoietic stem cell transplantation

Table 2. Number of Subjects With the Most Frequently Observed Sinopulmonary Manifestations According to the Primary Immunodeficiency Disorder Categories

PID Category	Pneumonia (n = 80)	Otitis media (n = 59)	Bronchiectasis (n = 28)	Asthma (n = 22)
Combined immunodeficiencies	32 (49.2)	22 (33.8)	7 (10.7)	9 (13.8)
Well-defined syndromes with immunodeficiency*	12 (26.6)	7 (15.5)	2 (4.4)	5 (11.1)
Predominantly antibody deficiencies	21 (60)	21 (60)	12 (34.2)	6 (17.1)
Diseases of immune dysregulation	8 (26.6)	8 (26.6)	3 (10)	2 (6.6)
Congenital defects of phagocyte number, function or both	3 (21.4)	1 (7.1)	0 (0)	0 (0)
Autoinflammatory disorders†	0 (0)	0 (0)	0 (0)	0 (0)
Complement deficiencies	4 (44.4)	0 (0)	4 (44.4)	0 (0)

Data are n (%).

* Wischott-Aldrich syndrome, DiGeorge syndrome, STAT3 deficiency, ataxia-telangiectasia, and hepatic veno-occlusive disease with immunodeficiency.

† interleukin-10 deficiency.

PID = primary immunodeficiency disorder

were isolated during 46 pneumonia episodes (42.5%) as follows: cytomegalovirus (16 episodes), *Pneumocystis jirovecii* (9 episodes), *Klebsiella pneumoniae* (3 episodes), adenovirus, parainfluenza Epstein-Barr virus, H1N1, and *Aspergillus fumigatus* (2 episodes each), respiratory syncytial virus, herpes simplex virus, varicella, rhinovirus, *Enterobacter cloacae*, *Stenotrophomonas*, *Enterococcus faecalis*, and *Streptococcus pneumoniae* (one episode each). Table 3 shows miscellaneous sinopulmonary manifestations according to specific primary immunodeficiency disorder diseases.

There were 57 deaths (28%) during the study period. Twenty-four deaths (42%) were due to pulmonary complications as follows: pneumonia (16 subjects, 8%), pulmonary hemorrhage (6 subjects, 3%), and aspiration pneumonia (2 subjects, 1%).

Discussion

This study presents the frequency and spectrum of sinopulmonary complications among subjects with primary immunodeficiency disorders. Furthermore, it describes the distribution of specific sinopulmonary manifestations according to primary immunodeficiency disorder categories as well as the sequence of appearance of various sinopulmonary complications in relation to the primary immunodeficiency disorder diagnosis.

Sixty-three percent of the reported subjects suffered from various sinopulmonary complications, with approximately 1.5 manifestations/subject. More than half of the complications were among the presenting symptoms. Sinopulmonary complications continued to occur even after establishment of the primary immunodeficiency disorder

Table 3. Miscellaneous Sinopulmonary Manifestations According to Specific Primary Immunodeficiency Disorder Diseases

Sinopulmonary Manifestations	PID Diagnosis (n)
Sinusitis (n = 12)	ZAP-70 deficiency (1)
	Agammaglobulinemia with no B cells (1)
	AID deficiency (3)
	Selective IgA deficiency (3)
	CVID (3)
	STAT3 deficiency (1)
Interstitial lung diseases (n = 6)	RAG2 deficiency (1)
	Agammaglobulinemia with no B cells (1)
	CVID (1)
Pulmonary nodules (n = 4)	Immunodysregulation (1)
	PAP (2)
	CGD (1)
	DiGeorge syndrome (1)
	Immunodysregulation (1)
Lymphocytic interstitial pneumonitis	AID deficiency (1 patient)
	STAT5b deficiency (2)
Laryngeal web	DiGeorge syndrome (1)
Sunglottic stenosis	DiGeorge syndrome (1)
Pulmonary graft versus host disease	MHC II deficiency and stem cell transplant (1)
Allergic bronchopulmonary aspergillosis	DOCK8 deficiency (1)
Alveolar haemorrhage	SCID and stem cell transplant (1)
Aspiration pneumonia	SCID (2)

PID = primary immunodeficiency disorder
 ZAP-70 = zeta-chain-associated protein kinase 70
 AID = activation-induced deaminase
 CVID = common variable immunodeficiency
 STAT3 = signal transducer and activator of transcription 3
 RAG2 = recombination-activating gene 2
 PAP = pulmonary alveolar proteinosis
 STAT5b = signal transducer and activator of transcription 5b
 MHC = major histocompatibility complex
 DOCK8 = dedicator of cytokinesis 8
 SCID = severe combined immunodeficiency

diagnosis. This observation is in agreement with previous findings showing that despite the use of appropriate treatment, many subjects with primary immunodeficiency disorder continue to develop acute and chronic infections as well as many noninfectious complications.^{25,26} Lung diseases significantly impacted the quality of life of subjects with some types of primary immunodeficiency disorder²⁷ and were common causes of death in another group of subjects with primary immunodeficiency disorder.²⁸ Forty-two percent of the deaths that occurred during the current study period were due to sinopulmonary complications. Accordingly, pulmonologists should play an active role in the care of patients with primary immunodeficiency disorder. These patients should also be closely monitored and screened regularly for lung complications so that early

Table 4. Warning Signs of Primary Immunodeficiencies in Children

≥4 new ear infections within 1 y
≥2 serious sinus infections within 1 y
≥2 mos. on antibiotics with little effect
≥2 episodes of pneumonia within 1 y
Failure of an infant to gain weight or grow normally
Recurrent, deep skin or organ abscesses
Persistent thrush in mouth or fungal infection on skin
Need for intravenous antibiotics to clear infections
Two or more deep-seated infections, including septicemia
A family history of primary immunodeficiency

If a child is affected by ≥2 warning signs, he or she should be examined for possible primary immunodeficiency.

and aggressive interventions can be initiated to avoid significant morbidity and mortality.

Sinopulmonary complications were more common in subjects with predominantly antibody deficiencies compared with the other categories. A possible explanation for this is that the disease severity in this primary immunodeficiency disorder category is less compared with other primary immunodeficiency disorder categories, and thus patients live longer with a greater chance of developing various complications. Another explanation for such a finding is that in comparison with other primary immunodeficiency disorder categories, patients with predominantly antibody deficiencies have very low IgA, which is important for mucosal immunity as in the respiratory and gastrointestinal tracts. As expected, infections were the most common sinopulmonary manifestations in our cohort, which is consistent with previous reports.²⁹ In a previous study, 14% of the subjects who presented with recurrent pneumonia were found to have an underlying immune disorder.³⁰ Because respiratory infections are common in general, physicians should be alerted about the proper indications to work up patients for the possibility of primary immunodeficiency disorders. For this purpose, the Jeffery Model Foundation has published 10 warning signs³¹ (Tables 4 and 5). However, these signs should only be used as guidance. For example, a neonate presenting with a first episode of pneumonia caused by *P. jirovecii* should be worked up for possible primary immunodeficiency disorder without waiting for the second episode to develop.

We were able to identify the causative pathogen in 46 episodes of pneumonia, facilitating the use of targeted antimicrobial agents. As observed in our cohort, the pathogens that cause respiratory infectious complications in primary immunodeficiency disorder display a typical spectrum according to the immune defect.²⁹ This observation should aid in the diagnostic approach in an attempt to identify a particular type of primary immunodeficiency disorder. For example, patients with combined immunodeficiencies are prone to develop respiratory infections

Table 5. Warning Signs of Primary Immunodeficiencies in Adults

<p> ≥ 2 new ear infections within 1 y ≥ 2 new sinus infections within 1 y, in the absence of allergy 1 pneumonia/y for more than 1 y Chronic diarrhea with weight loss Recurrent viral infections (colds, herpes, warts, condyloma) Recurrent need for intravenous antibiotics to clear infections Recurrent, deep abscesses of the skin or internal organs Persistent thrush or fungal infection on the skin or elsewhere Infection with normally harmless tuberculosis-like bacteria A family history of primary immunodeficiency </p>
<p>If an adult is affected by ≥ 2 warning signs, he or she should be examined for possible primary immunodeficiency.</p>

caused by a wide range of bacteria, fungi, and viruses, whereas patients with predominantly antibody deficiencies are at risk of developing bacterial respiratory infections. Patients with phagocytic defects, however, are prone to developing respiratory infections caused by bacteria and fungi.

Bronchiectasis affected only 13.8% of the presented subjects. It was more common in predominantly antibody deficiencies (34.2%), which is in agreement with previous studies, and affected 37% of the subjects with common variable immunodeficiency³² and 32% of those with X-linked agammaglobulinemia.²⁷ In a recent review,³³ primary immunodeficiency disorder was the cause of bronchiectasis in 16% of non-cystic fibrosis subjects. Accordingly, any patient who presents with bronchiectasis should be worked up for primary immunodeficiency disorder. Additionally, patients with primary immunodeficiency disorder, particularly those suffering from predominantly antibody deficiencies, should be regularly screened for bronchiectasis using high-resolution computed tomography.³⁴

Asthma affected only 11% of our cohort, whereas its prevalence in our population was found to exceed 15%.³⁵ This could be due to underreporting of symptoms or underdiagnosis. Four subjects presented with pulmonary nodules, which were associated with granulomatous diseases affecting other organs (spleen, liver, and gut). Two subjects with signal transducer and activator of transcription 5b deficiency had lymphocytic interstitial pneumonitis, which is a known complication of this disease.³⁶

There are some limitations of this work despite the fact that it is a longitudinal prospective study. The age of the development of sinopulmonary complication and the time of occurrence after establishing primary immunodeficiency disorder diagnosis are not available in our registry data. Furthermore, not all subjects with infectious sinopulmonary complication had extensive testing to identify the causative microbial agents. In addition, screening spirometry and high-resolution computed tomography of the chest

were not done in all subjects suffering from predominantly antibody deficiencies.

Conclusions

In the present study, we presented the frequency of sinopulmonary manifestations in subjects with primary immunodeficiency disorder who were included in a national registry prospectively over a period of 10 y. It is important to perform similar studies in subjects with primary immunodeficiency disorder who are of different ethnicities and from various geographic areas as well as in subjects with specific primary immunodeficiency disorder diseases. This strategy will facilitate a better understanding of pathophysiologic factors underlying the occurrence of sinopulmonary complications in primary immunodeficiency disorder such that appropriate measures can be undertaken in a timely manner to avoid morbidity and mortality. Due to the high frequency and severity of such complications, pulmonologists should play an important role in the management of patients with primary immunodeficiency. This role will be facilitated by an awareness of the classification and mechanisms of primary immunodeficiency disorder and their associated pulmonary complications.

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