

# Primary Antibody Deficiencies at Queen Rania Children Hospital in Jordan: Single Center Experience

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## ABSTRACT

**Background:** Primary antibody deficiency, the most common primary immunodeficiency disorder, represents a heterogeneous spectrum of conditions caused by a defect in any critical stage of B cell development and is characterized by impaired production of normal amounts of antigen-specific antibodies. **Objective:** This retrospective study aimed at description and analysis of demographic, clinical, immunological features and complications of subjects diagnosed with primary antibody deficiency at a referral center in Jordan. **Methods:** The medical records of pediatric patients who were diagnosed as primary antibody deficiency (PAD) during the period from January 2006 to June 2013 were reviewed. Patients were diagnosed as PADs based on the Pan-American Group for Immunodeficiency (PAGID) and the European Society for Immunodeficiency (ESID) diagnostic criteria. **Results:** A total number of 53 patients with PAD were identified; 37(70%) males and 16(30%) females, 16(30%) patients with congenital agammaglobulinemia, 16(30%) patients with common variable immunodeficiency, 4(7.5%) patients with IgG subclass deficiency, 10(19%) cases with transient hypogammaglobulinemia of infancy and 7(13.5%) patients as undefined PAD. The most common infection among patients was pneumonia (62%); followed by suppurative otitis media in 49% of patients. Cytopenia was the most noted autoimmune association and was found at prevalence of 22 %, other autoimmune associations (17%) including inflammatory arthritis, discoid lupus, inflammatory bowel disease, vasculitis and celiac disease. The prevalence of long-term complications was 58%, the most frequent ones were; stunted growth in 13%, bronchiectasis and lymphoproliferation in 11% for each. **Conclusions:** Our results indicated that congenital agammaglobulinemia and common variable immunodeficiency are the most frequent primary antibody deficiency in our patients. The awareness of families, general population as well as primary health physicians is crucial in the establishment of early diagnosis and prompt commencement of appropriate therapy for PADs.

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## INTRODUCTION

Primary immunodeficiency disorders (PIDs) are uncommon disorders of the immune system characterized by insufficiently mounting protective immune response, leading to an increased susceptibility to infections (1). Primary antibody deficiency (PAD), the most common PID, represents a heterogeneous spectrum of conditions caused by a defect in any critical stage of B cell development and characterized by impaired production of normal amounts of antigen-specific antibodies (2-4). Based on the International Union of Immunological Societies (IUIS) classification criteria, predominantly antibody deficiency disorders are classified into congenital hypogammaglobulinemia, common variable immunodeficiency and other related disorders with reduction in at least two immunoglobulin isotypes and low or normal B cell, Hyper-IgM disorders, selective IgA deficiency, IgG subclass deficiency, selective antibody deficiency and transient hypogammaglobulinemia of infancy (5). Despite the heterogeneity in the clinical spectrum of diseases, high rate of chronic or recurrent infections is shared by all clinically significant PADs; pyogenic encapsulated bacteria are the most commonly isolated pathogens (6). Respiratory tract infections are the prominent cause of hospitalization followed by gastrointestinal infections (7). It is generally considered that patients with defective antibody function have significantly lower risk of viral infections, in contrast to bacterial, with notable exception of Enteroviruses (8). In Addition to infections, complications including malignancy, inflammatory and autoimmune diseases may be seen (9).

PADs should be suspected in all patients presenting with recurrent infections that have unusual severity or lack response to therapy (6), particularly if presented after the fourth to sixth month of life when maternally acquired antibodies have declined or disappeared (10). Antibody replacement therapy and antimicrobial therapy play a central role in managing patients with PAD to prevent and treat infections and infection-related complications, in addition regular surveillance for non-infectious complications such as malignancy and autoimmunity is recommended (6). Delay in diagnosis may have negative impact on prognosis. So, increased awareness to PADs is crucial for prompt diagnosis and initiation of therapy to prevent long term complications.

To the best of our knowledge, Queen Rania Children Hospital is one of the largest referral centers for primary immunodeficiency disorders in Jordan. Our study is a retrospective study describing the clinical spectrum of primary antibody deficiency in our hospital. We are aiming to increase the awareness of primary care physicians for these rare disorders and underscore the necessity for early referral.

## MATERIALS AND METHODS

**Subjects.** The medical records of pediatric patients who were diagnosed as primary antibody deficiency (PAD) during the period from January 2006 to June 2013 were reviewed. These patients were referred to Immunology Division at Queen Rania Children Hospital from different hospitals and clinics in Jordan. Patients were diagnosed as PADs based on the Pan-American Group for Immunodeficiency (PAGID) and the European Society for Immunodeficiency (ESID) diagnostic criteria (14), all patients meet the criteria for probable diagnosis as the molecular diagnosis is not available at our institute, the PAD disorders had been diagnosed and classified into five

categories; congenital agammaglobulinemia (CA) whether X-linked or autosomal recessive, common variable immunodeficiency (CVID), IgG subclass deficiency (IgGSCD), transient hypogammaglobulinemia of infancy (THI) and undefined PAD. We excluded patients with selective IgA deficiency and patients with T cell deficiency like severe combined immunodeficiency and Wiskott-Aldrich syndrome. We designed an intake data sheet which contained the patients' demographic information including name, age at clinical presentation, age at diagnosis at our clinic and age at last follow up, diagnosis, family history of PID, infections, associated autoimmune disease and allergy, and complications.

**Immunological Tests.** The initial immunological work up at time of referral to immunology division included serum immunoglobulin G, M and A, IgG subclass titers, isohemagglutinin with blood group, antibody response following immunization with tetanus vaccine, complete blood counts with differential, and lymphocytes subsets by flow cytometry. Serum immunoglobulin levels were done by immune-diffusion test and lymphocyte subsets were done by flow cytometry with monoclonal antibodies against CD3, CD4, CD8, CD19, and CD16+56 at Princess Iman Center for Research and Laboratory Sciences.

## RESULTS

**Patients' Characteristics.** As indicated in Table 1, the total number of patients was 53 patients with PAD; 37 (70%) males and 16 (30%) females, 16(30%) patients with CA, 16 (30%) patients with CVID, 4 (7.5%) patients with IgGSCD, 10 (19%) cases with THI and 7 (13.5%) patients with undefined PAD.

**Table 1. Primary antibody deficiency patients' characteristics.**

PAD	CA	CVID	IgGSCD	THI	undefined	All
Male N (%)	12 (22.6)	11 (20.7)	2 (3.7)	6 (11.3)	6 (11.3)	37 (70)
Female N (%)	4 (7.5)	5 (9.4)	2 (3.7)	4 (7.5)	1 (1.8)	16 (30)
Total (%)	16 (30)	16 (30)	4 (7.5)	10 (19)	7 (13.5)	53 (100)
Family history (%)	5 (9.4)	4 (7.5)	0 (0.0)	0 (0.0)	1 (1.9)	10 (18.9)
Age at presentation in years (Mean ± SD)	1± 0.4	2.7 ± 0.9	3.8 ± 0.8	1 ± 0.4	2.6 ± 1.8	2.6 ± 1.3
Age at diagnosis in years (Mean ± SD)	2.8 ± 1.8	5.1 ± 2.3	6.1 ± 1.6	1.6 ± 0.4	5.0 ± 3.1	4.7 ± 2.5
Diagnostic delay in years Median (Range)	1.8(0.5-5)	2.5(0.8-6)	2.3(1-3)	0.6(0.3-0.9)	2.4(0.2-5)	2.3(0.2-6)

PAD: primary antibody deficiency, CA: congenital agammaglobulinemia, IgGSCD: IgG subclass deficiency, THI: transient Hypogammaglobulinemia.

The patients' age at study ranged from 6 months to 14 years, the mean age at clinical presentation was 2.6 years, and at time of diagnosis was 4.7 years with 2.3 years as mean diagnostic delay which is defined as the time elapsed from the onset of clinical presentation until the time of diagnosis, the longest was in CVID group at 2.5 years while the shortest was in THI group at 7 months. The mean duration of follow up was 3.3 years ranged from 6 months to 12 years. The family history of recurrent infections or unexplained deaths was reported in 7 patients who accounted for 19% of the total PADs; 4 patients had a family member with CVID, 5 patients had a family member with congenital agammaglobulinemia and one patient had a family member with an undefined PAD group.

**Infections and Laboratory Data.** There was a diversity of infection sites reported at initial presentation and during follow up as shown by Table 2.

**Table 2. Number and percentage of primary antibody deficiency cases presented with the listed infections.**

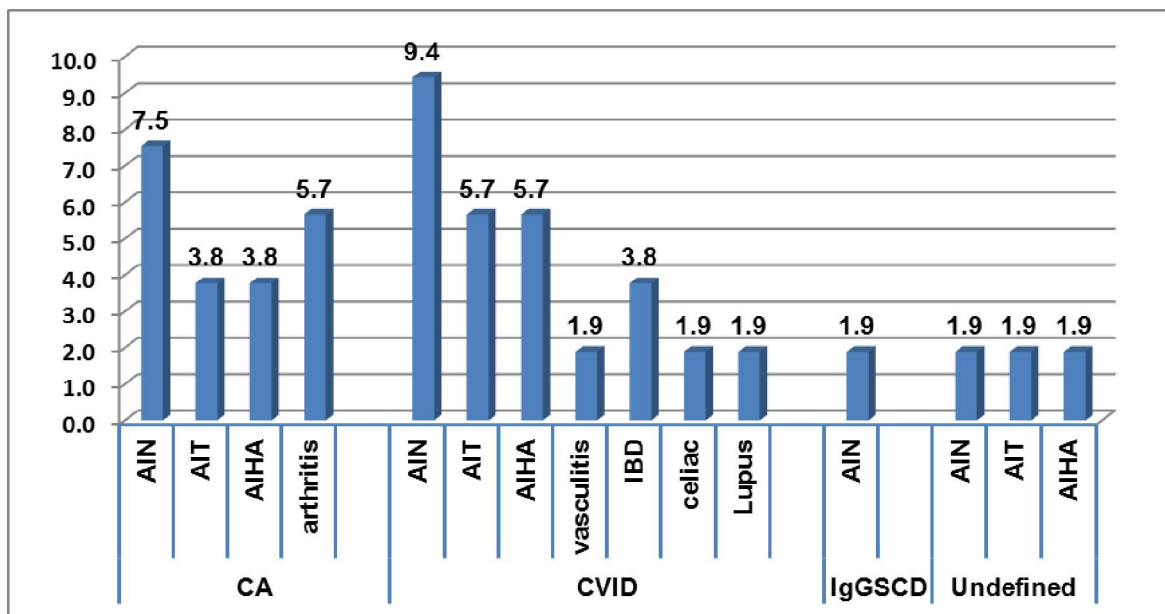
Infection	CA	CVID	IgGSCD	THI	undefined	Total N (%)
Pneumonia	12	9	4	6	2	33 (62.3)
Otitis Media	10	5	3	5	3	26 (49.1)
Sinusitis	6	7	2	1	2	18 (34.0)
Enteritis	3	5	-	2	3	13 (24.5)
Lymphadenitis	3	3	-	3	-	9 (17.0)
Septicemia	5	4	-	-	-	9 (17.0)
Meningitis	1	2	-	1	4	8 (15.1)
Mastoiditis	3	3	-	1	0	7 (13.2)
Cellulitis	1	2	-	-	-	3 (5.7)
Necrotizing fasciitis	1	2	-	-	-	3 (5.7)
Oral Candidiasis	-	2	-	-	-	2 (3.8)
Impetigo	1	-	-	1	0	2 (3.8)

PAD: primary Antibody deficiency, CA: congenital agammaglobulinemia, IgGSCD: IgG subclass deficiency, THI: transient hypogammaglobulinemia.

The most common infection was pneumonia (62%), followed by suppurative otitis media in 49% of patients complicated by mastoiditis in 7 (13%) patients, one third of patients had sinusitis as an initial presentation of PADs, more than half of sinusitis persisted as chronic rhino-sinusitis even with broad spectrum antibiotics. Twenty-five percent of patients had one or more episode of infectious enteritis; *Rotavirus*, *Giardia lamblia*, *Salmonella species* and *Cryptosporidium* were the most common isolated microorganisms. Serious infections included bacterial meningitis in 15% of cases, septicemia in 17%, mostly in those who were hospitalized for febrile neutropenia, and necrotizing fasciitis in 5.7%. The least common infections were impetigo and oral candidiasis at 3.8% for each.

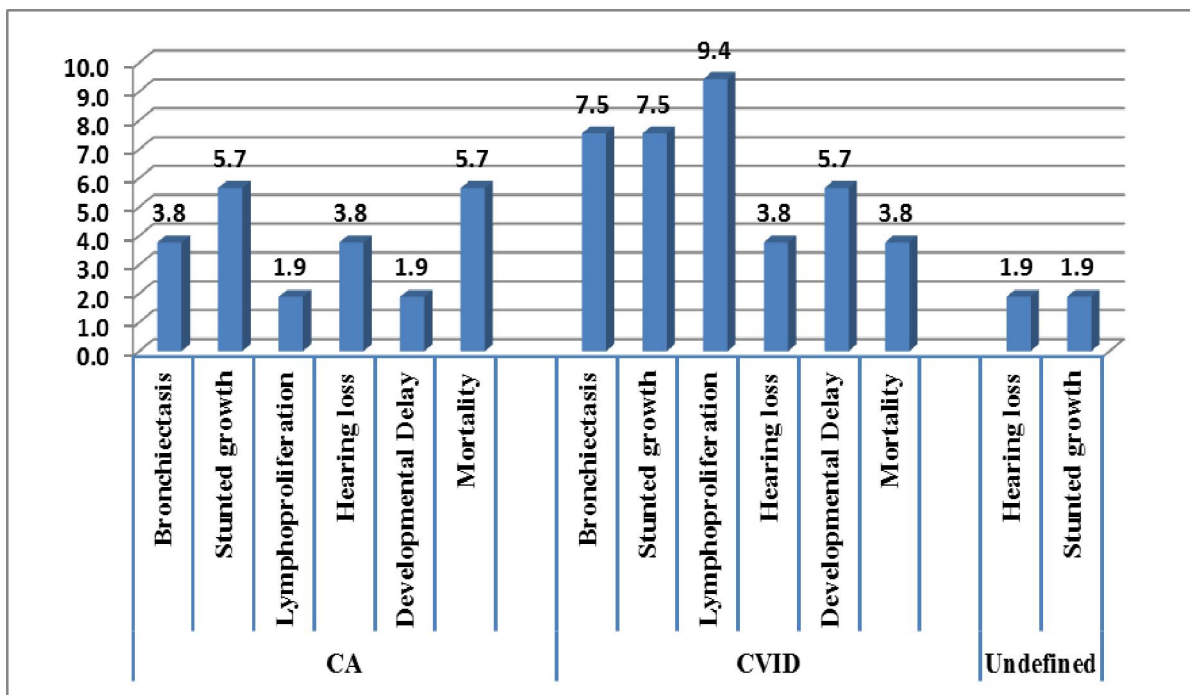
Mean serum IgA, IgM and IgG levels at time of diagnosis were 7.6, 21.7, and 94.4 mg/dl, respectively. All patients had at least one immunoglobulin isotype or IgG subclass level that was 2 SD below the mean for age at time of initial assessment except 4 patients who were referred with recurrent infections (2 as recurrent pneumococcal meningitis), and found to have normal immunoglobulin levels but showed complete absence of infections on immunoglobulin replacement therapy on long-term follow up, of note our lab does not have specific anti-pneumococcal antibody titers testing. Except THI, all patients received long-term intravenous immunoglobulin (IVIg) as replacement therapy at dose range 400-500 mg/kg every 3-4 weeks to keep IgG trough levels at 500-700 mg/dl. B cell count was normal in two third, low in 8% and absent (<2% of absolute lymphocytes) in 30% of patients.

**Associated Autoimmune Diseases.** Cytopenias were the most noted autoimmune association at 22 % (n=12), of note patients may have one or more autoimmune feature as Figure 1 shows.



**Figure1.** Percentages of associated autoimmune features in primary antibody deficiencies. AIN: autoimmune neutropenia, AIT: autoimmune thrombocytopenia, AIHA: autoimmune hemolytic anemia, IBD: inflammatory bowel disease. CA: congenital agammaglobulinemia, IgGSCD: IgG subclass deficiency, CVID, etc.

Half of associated autoimmune diseases were reported in CVID patients, the most frequent cytopenia was neutropenia, which resolved in most patients on IVIG replacement therapy, but on the other hand it was the leading cause for hospitalization for few patients with serious infection, other cytopenias included thrombocytopenia and autoimmune hemolytic anemia found in six cases. Four patients had inflammatory arthritis, 3 with CA and one with CVID. In addition to cytopenias, five CVID patients had other autoimmune diseases; 2 patients had inflammatory bowel disease (IBD) like enteropathy, one patient had discoid lupus, but did not show the full blown picture of lupus, one patient had celiac disease, and one patient had cutaneous leukocytoclastic vasculitis.



**Figure 2.** Complications and mortality percentages in primary antibody deficiencies.

**Complications and Mortality.** The prevalence of long-term complications was 58% as Figure 2 shows, the most frequent were; stunted growth in 15% (n=8) patients, bronchiectasis in 11% (n=6), lymphoproliferation in 11% (n=6) and hearing loss in 9% (n=5), two third of the complications occurred in CVID group. Mortality rate was 9% (n=5), 3 cases with congenital agammaglobulinemia and 2 cases with CVID, severe infection was the leading cause of death in four cases, and one case of CVID died secondary to refractory EBV induced hemophagocytic lymphohistiocytosis (HLH). Allergic disorders were observed in 26% (n=14) of cases, asthma, atopic dermatitis and allergic rhinitis were the most frequent forms.

## DISCUSSION

We described the clinical spectrum of 53 cases of primary antibody deficiency intending to increase the awareness of primary health physicians and other medical personnel for these rare disorders. Up to the best of our knowledge, this is the largest review for patients diagnosed with PAD in Jordan. Our hospital is considered as one of the largest referral centers in Jordan for PIDs. However, the number in this review does not actually reflect all patients in Jordan as some patients are managed in other hospitals; others are still undiagnosed and managed for their recurrent infections by general practitioners and some were unfortunate and died elsewhere before referral to a tertiary care can be made. The sex distribution showed that male was affected as twice as female. This is consistent with data published in previous studies (7,11,12). Ghatmann *et al.* showed that boys are affected much more frequently than girls in PID even if X-linked diseases are excluded (2). Higher male to female ratio has been seen in other region (13). We reported family history of either PAD or recurrent infections in 19% of our patients. It was recurrent infections and unexplained death in maternal cousins of five CA patients that were pointing to X-linked inheritance.

The ESID/PAGID diagnostic criteria were used to make the diagnosis (14). The diagnosis of PADs was not definitive because neither genetic nor molecular diagnosis is feasible at our hospital. Although the most reliable method of making a diagnosis of immunodeficiency is mutation detection, sufficiently distinctive clinical and lab data, if coupled with a relevant family history can frequently make a diagnosis with very high certainty (15). In addition, the proportion of molecular diagnosis varied among diseases; collectively 31% of patients had their affected gene detected in a previous study (16). We found that CA and CVID were the most common phenotypes with the same frequency accounting collectively for more than half of the patients (30% for each). Our data is in agreement with data from Ireland where CVID and XLA have the same number (17), and comparable to those from Oman (XLA 43% and CVID 30%). Data from Taiwan, Iran, and Australia, showed that CVID is the most common type of PAD followed by XLA (48% and 22% respectively in Iran) (11,12,18). This discrepancy may be related to the fact that our registry included only patients who are 14 year-old and less, which may limit the number of CVID patients who usually present in the second or third decade (24). Congenital agammaglobulinemia, presented earlier, is the most genetically determined PAD (13). Selective IgA deficiency is the most common primary immunodeficiency (1:700 worldwide); most patients are asymptomatic and diagnosed accidentally (19,20). Therefore, we excluded this disorder because the actual number will be underestimated. Around 13% of our patients fell in the undefined category. Two types of patients have been seen in this category; those with recurrent pneumococcal infections and normal Ig isotypes suspecting specific antibody deficiency (SAD) after exclusion of other differential diagnosis, and those who have recurrent infections with increased IgM and decreased both IgG and IgA suspecting Hyper-IgM syndrome. In our hospital, anti-pneumococcal antibodies detection is of limited availability and determination of AID and UNG mutations are not available; to confirm the diagnosis of SAD or Hyper-IgM Syndrome with isolated B cell defect respectively.

Despite the availability of immunologic work up, considerable diagnostic delay is still present (21). Our data showed that median diagnostic delay was 2.3 years (range 0.2 to 6 years); while the longest delay was seen in CVID patients, diagnosis of CA patients had delayed by 1.8 year. In reviewing patients from England, Seymour *et al.* showed

mean diagnostic delay of 4.4 years (median 2 years) (21). The median age at onset of symptoms in patients with CVID from Iran was 2 years with diagnostic delay of 5 years (22). In German registry, Ghathmann *et al.* showed a median diagnostic delay of 1 and 4 years for agammaglobulinemia and CVID respectively. Having a relatively shorter diagnostic delay may be related to the nature of our cohort which is a restricted pediatric population.

Pneumonia (in 60%) was the most common type of infection seen at presentation followed by suppurative otitis media, while gastrointestinal infections were experienced by only one fourth of the patients. Sinopulmonary infections have been the most common in similar previous studies (12,13,18). It reflects the nature of the disease in which recurrent sinopulmonary infections are seen in more than 90% of patients (23).

Autoimmune cytopenia was the most common autoimmune disease found in our patients who were mostly in CVID group. Based on literature review, Podjasek and Abraham showed that autoimmune cytopenia are the most common (20-50%) among the autoimmune manifestations reported in CVID (24). IBD was seen in two CVID patients. Unlike other PAD, gastrointestinal diseases are more common in CVID owing to the T cell dysfunction which may contribute to gastrointestinal disease (9).

The most commonly encountered complication seen in our patients was stunted growth followed by bronchiectasis. Complications were mostly seen in patients with CVID, particularly with delayed diagnosis. In series from Taiwan, Wang *et al.* reported bronchiectasis to be the most common complication followed by short stature, and complications were mostly seen in those who were not treated properly (12).

The use of prophylactic antibiotics and/or immunoglobulin replacement therapy is considered the mainstay of treatment in PAD (25). Use of IVIG 300-400 mg/kg/3-4 weeks has significantly reduced the rate of respiratory tract infections in CVID patients (26). The mean IgG level at the time of diagnosis for our patients was 94 mg/dl. Prophylactic antibiotics and IVIG were used in all patients in whom the required trough level (500-700 mg/dl) was achieved. All patients showed significantly reduced number of hospitalization after initiation of IVIG replacement therapy.

Mortality rate of 9% was reported in our patients; severe infection was the leading cause of death, but no particular microorganism could be detected as a frequent cause. One interesting findings in our study is that HLH was a leading cause of death in one patient. Mortality rate in previous studies has been reported between 14-17% but for all PID patients (13,18,27).

Our study is limited by its retrospective nature and the lack of molecular diagnosis. We also could not differentiate the disorders type in undefined group. In Conclusion The awareness of families, general population as well as primary health physicians is crucial in the establishment of early diagnosis and prompt commencement of appropriate therapy for PADs.

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