

Overview of humoral immunodeficiencies with emphasis on specific antibody deficiency: A study at a tertiary care center

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ABSTRACT

Objective: To identify the spectrum of humoral immunodeficiencies, particularly Specific Antibody Deficiency (SAD), and evaluate their clinical and immunophenotypic characteristics in a tertiary care setting.

Material and Methods: This analytical cross-sectional study was conducted at the Department of Immunology, Armed Forces Institute of Pathology (National University of Medical Sciences), Rawalpindi, Pakistan, from January 2020 to December 2024. Patients of all ages meeting ESID/PAGID criteria for agammaglobulinemia, selective IgA deficiency (SIgAD), common variable immunodeficiency (CVID), transient hypogammaglobulinemia of infancy (THI), or specific antibody deficiency (SAD) were included. Pneumococcal vaccine responses were assessed using WHO ELISA. Serum IgG, IgA, and IgM were measured by radial immunodiffusion, total IgE by ELISA, and B-cell subsets by flow cytometry (FACSCanto II™, BD Biosciences). Data were analyzed using SPSS version 27, with $p < 0.05$ considered significant.

Results: Forty-five patients had humoral PID: agammaglobulinemia (44.4%), SIgAD (26.7%), CVID (13.3%), SAD (11.1%), and THI (4.4%). SAD patients had the longest diagnostic delay (1.2 years; IQR 1.0–2.0), latest onset (8.0 years; IQR 5.5–10.0), and 80% prevalence of asthma and atopy. Switched memory B cells were significantly lower in SAD than controls (4.5 ± 1.67 vs. 9.4 ± 2.94 ; $p = 0.003$; Cohen's $d = -1.835$).

Conclusion: Agammaglobulinemia was the most prevalent humoral PID, while SAD comprised 11.1% of cases and exhibited distinct clinical and immunophenotypic features. Functional antibody testing and B-cell phenotyping are important for early diagnosis of SAD in Pakistan.

Keywords: B-Lymphocytes, Immunodeficiency, Immunophenotyping, Pneumococcal vaccines, Specific antibody deficiency.

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INTRODUCTION

Inborn errors of immunity, historically termed primary immunodeficiencies (PIDs), are heterogeneous disorders caused by defects in immune development or function. Predominantly antibody deficiencies are the most frequently recognized group in clinical practice and range from profound failure of B-cell development to impaired immunoglobulin production or vaccine-specific responses [1,2]. Patients commonly present with recurrent sinopulmonary infection, but autoimmunity, allergy, inflammation, lymphoproliferation, and malignancy may also occur [3].

Specific antibody deficiency (SAD) is characterized by recurrent infection and an inadequate antibody

response to polysaccharide antigens despite age-appropriate total immunoglobulin concentrations [4-6]. Its laboratory profile is less conspicuous than agammaglobulinemia or common variable immunodeficiency (CVID), so diagnosis depends on paired pre- and post-vaccination serotype-specific antibody testing. Differences in vaccines, serotypes, assay platforms, age thresholds, and response definitions complicate comparisons across centers [5, 6].

Published frequencies vary with the population tested. A Korean adult cohort selected for suspected or confirmed antibody deficiency identified SAD in 11 of 47 participants (23.4%) [7]. Pakistani data are limited and mostly describe the broader PID spectrum; an AFIP series reported humoral deficiencies in 13 of 60 patients (21.6%) and respiratory infection in 46 (76.6%) [8], while a later Pakistani series reported humoral defects in 51 of 185 patients (28%) [9]. These selected referral cohorts do not estimate population prevalence, but they show the clinical burden and the scarcity of subtype-specific local evidence.

No Pakistani study identified in the available literature specifically quantified SAD within a defined humoral-

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PID cohort while also comparing B-cell subsets with healthy controls. Functional antibody testing is not routinely available in many centers, and patients with normal total immunoglobulin concentrations may therefore remain unclassified. The local frequency, diagnostic delay, clinical correlates, and immunophenotypic pattern of SAD remain uncertain. This study was therefore conducted at a national referral center with functional antibody and flow-cytometry facilities to describe the spectrum of confirmed humoral PIDs, determine the proportion classified as SAD, compare SAD with other humoral PIDs, and compare selected B-cell subsets between SAD patients and healthy controls. The results may help define locally relevant diagnostic priorities and provide preliminary estimates for larger, prospectively powered studies.

MATERIAL AND METHODS

This analytical cross-sectional study was conducted at the Department of Immunology, Armed Forces Institute of Pathology (AFIP)/NUMS, Rawalpindi, after the approval of institutional ethical review board (IERB # FC/IMM17-27/IRB/19/314 dated 26th June 2019) from 1st January 2020 to 30th December 2024. Sample size was calculated using WHO formula, taking the anticipated population proportion 2.3% [10], with 95% confidence interval and 0.05 absolute precision. Because this was a single-center referral study of a rare, selected disorder, all 45 eligible patients identified during the study period were included (census sampling); no patients were excluded because of a target sample-size shortfall. Patients of any age evaluated for suspected humoral PID were eligible if they had a confirmed diagnosis of agammaglobulinemia, selective IgA deficiency (SIgAD), common variable immunodeficiency (CVID), specific antibody deficiency (SAD), or transient hypogammaglobulinemia of infancy (THI), according to the ESID Registry Working Definitions for clinical diagnosis of inborn errors of immunity (2019) [2]. Secondary immunodeficiency due to malignancy, nephrotic syndrome, protein-losing enteropathy, or another acquired cause was excluded, as were combined/cellular immunodeficiencies, including severe combined immunodeficiency and defined T-cell defects.

Demographic and clinical variables recorded for the 45 patients were age, sex, age at symptom onset, age at diagnosis, diagnostic delay, family history of PID, parental consanguinity, diagnosis, recurrent otitis media, respiratory tract infection, failure to thrive, asthma/atopy, and enteropathy. Serum IgG, IgA, and IgM were quantified by radial

immunodiffusion (The Binding Site, Birmingham, UK), and total IgE was measured by ELISA (BioCheck, Foster City, CA, USA).

Functional antibody responses were assessed by measuring pre- and post-Prevenar 13® (PCV-13) serum anti-pneumococcal IgG titers using WHO ELISA for seven serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F). SAD was operationally defined as recurrent infection with normal quantitative immunoglobulins and an inadequate response to polysaccharide pneumococcal antigens; an adequate response required a fourfold rise in titers or a post-vaccine titer ≥ 1.3 $\mu\text{g/mL}$ to at least 70% of tested serotypes. This local operational definition was applied consistently because pneumococcal polysaccharide vaccine (PPV-23) testing was unavailable.

B-cell enumeration and immunophenotyping were performed in patients and age-matched healthy controls using flow cytometry (FACSCanto II™, BD Biosciences, San Jose, CA, USA) with monoclonal antibodies IgD-PE, CD19-APC, CD45-PerCP, and CD27-FITC (BD Biosciences, Pharmingen, Germany). EDTA-anticoagulated whole blood samples were processed following the standard Stain/Lyse/Wash protocol. The following subsets of peripheral CD19⁺ B-cells were identified: class-switched memory B cells (CD19⁺CD27⁺IgD⁻), memory B cells (CD19⁺CD27⁺), non-switched memory B cells (CD19⁺CD27⁺IgD⁺), and naïve mature B cells (CD19⁺CD27⁻IgD⁺).

Data were analyzed in SPSS version 27.0 (IBM Corp., Armonk, NY, USA). Categorical variables were summarized as n (%). Age was summarized as mean (SD). The Shapiro-Wilk test assessed the distributions of age at onset, age at diagnosis, diagnostic delay, naïve B-cell percentage, and switched-memory B-cell percentage. Because age at onset, age at diagnosis, and diagnostic delay were non-normal, their distributions were compared between the SAD (n=5) and non-SAD humoral-PID (n=40) groups using two-sided exact Mann-Whitney U tests. Two-sided Fisher exact tests were used to compare disease group (SAD vs non-SAD) with sex, family history, consanguinity, recurrent otitis media, respiratory tract infection, failure to thrive, asthma/atopy, and enteropathy; Fisher tests were selected because expected cell counts were below five. Independent two-sample t tests compared naïve and switched-memory B-cell percentages between SAD patients (n=5) and healthy controls (n=14); equal variances were used because Levene tests was non-significant. Mean differences, 95% CIs, and

Cohen's d with 95% CIs were reported. Negative d values indicate lower means in SAD; absolute d values of approximately 0.2, 0.5, and 0.8 were interpreted as small, moderate, and large. All tests were two-sided and $p < 0.05$ was considered statistically significant.

RESULTS

The patient cohort included 30 males (66.7%) and 15 females (33.3%) and had a mean age of 6.9 years (SD 8.2). Among the 45 patients, agammaglobulinemia was diagnosed in 20 (44.4%), SIgAD in 12 (26.7%), CVID in 6 (13.3%), SAD in 5 (11.1%), and THI in 2 (4.4%) (Table I). The 14 healthy controls were included only in the B-cell subset comparison and were not part of the 45-patient diagnostic cohort.

Patients with SAD had a median age at onset of 8.0 years (IQR 5.5-10.0), median age at diagnosis of 9.0 years (IQR 6.0-12.0), and median diagnostic delay of 1.2 years (IQR 1.0-2.0). The corresponding non-SAD values were 0.9 years (IQR 0.7-9.2), 1.2 years (IQR 0.8-10.2), and 0.3 years (IQR 0.2-1.0), respectively. None of these distributional comparisons was statistically significant (exact $p = 0.137$, 0.137 , and

0.073 ; Table II). Asthma/atopy occurred in 4 of 5 SAD patients (80.0%) versus 13 of 40 non-SAD patients (32.5%; $p = 0.060$). Respiratory tract infection occurred in 4 (80.0%) versus 25 (62.5%; $p = 0.641$), while recurrent otitis media occurred in 2 (40.0%) versus 29 (72.5%; $p = 0.166$). All categorical comparisons were non-significant by two-sided Fisher exact tests (Table II). Clinical manifestations are summarized in Table II and illustrated in Figure 1. Analysis of peripheral B-cell subsets showed a difference between patients with Specific Antibody Deficiency (SAD) and healthy controls. The percentage of naïve B cells ($CD19^+CD27^-IgD^+$) was lower in the SAD group, mean 59.6 (10.24) compared with controls, mean 65.0 (7.06), although this difference did not reach statistical significance ($p = 0.208$; Cohen's $d = -0.682$). In contrast, switched memory B cells ($CD19^+CD27^+IgD^-$) were significantly reduced in patients with SAD, mean 4.5 (1.67) relative to controls, mean 9.4 (2.94), with a statistically significant difference ($p = 0.003$) and a large observed effect size (Cohen's $d = -1.835$).

Table-I: Spectrum of humoral immunodeficiencies in the patient cohort.

Diagnosis	Frequency	Percent
Agammaglobulinemia	20	44.4
Selective IgA deficiency (SIgAD)	12	26.7
Common Variable Immunodeficiency (CVID)	6	13.3
Transient Hypogammaglobulinemia (THI)	2	4.4
Specific Antibody Deficiency	5	11.1
Total	45	100.0

Table-II: Demographic and clinical characteristics of SAD and non-SAD humoral-PID groups.

Characteristic	SAD (n=5)	Non-SAD PID (n=40)	p value
Sex			
Male	3 (60.0%)	27 (67.5%)	
Female	2 (40.0%)	13 (32.5%)	
Age at onset, median (IQR), years	8.0 (5.5-10.0)	0.9 (0.7-9.2)	0.137 ^b
Age at diagnosis, median (IQR), years	9.0 (6.0-12.0)	1.2 (0.8-10.2)	0.137 ^b
Diagnostic delay, median (IQR), years	1.2 (1.0-2.0)	0.3 (0.2-1.0)	0.073 ^b
Family history, yes	1 (20.0%)	7 (17.5%)	1.000 ^a
Consanguinity, yes	1 (20.0%)	19 (47.5%)	0.362 ^a
Clinical features			
Recurrent otitis media	2 (40.0%)	29 (72.5%)	0.166 ^a
Respiratory tract infection	4 (80.0%)	25 (62.5%)	0.641 ^a
Failure to thrive	1 (20.0%)	19 (47.5%)	0.362 ^a
Asthma/ atopy	4 (80.0%)	13 (32.5%)	0.060 ^a
Enteropathy	1 (20.0%)	18 (45.0%)	0.378 ^a

a. Two-sided Fisher exact test, b. Two-sided exact Mann-Whitney U test. Percentages use the column group as denominator. IQR, interquartile range; PID, primary immunodeficiency; SAD, specific antibody deficiency.

Table-III: B-cell subsets in SAD patients and healthy controls.

B-cell subset, %	SAD (n=5), mean (SD)	Control (n=14), mean (SD)	p-value ^a	Cohen's d (95% CI) ^b
Naïve ($CD19^+CD27^-IgD^+$)	59.6 (10.25)	65.0 (7.06)	0.208	-0.682 (-1.719 to 0.373)
Switched memory ($CD19^+CD27^+IgD^-$)	4.5 (1.67)	9.4 (2.94)	0.003	-1.835 (-3.006 to -0.625)

a. Independent two-sample t test with equal variances, b. Negative d indicates a lower mean in SAD. Approximate absolute-interpretation: 0.2 small, 0.5 moderate, 0.8 large. CI, confidence interval; SAD, specific antibody deficiency.

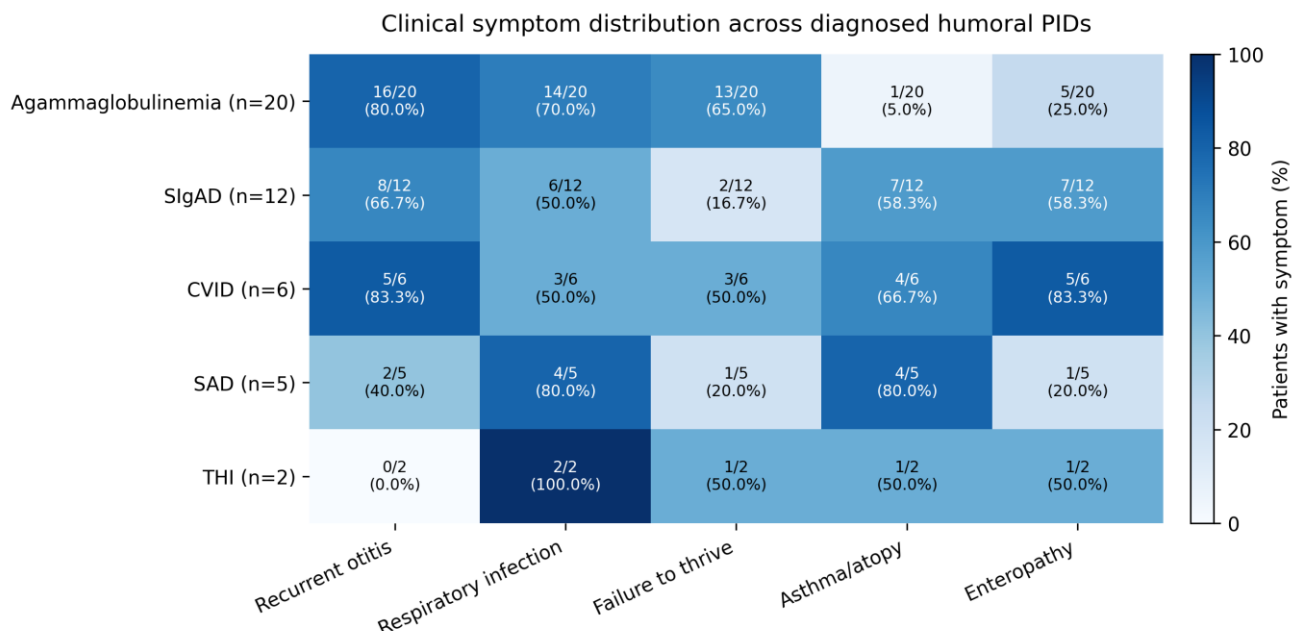


Figure-I: Clinical symptom distribution across the diagnosed humoral immunodeficiency groups.

DISCUSSION

In this single-center referral cohort, agammaglobulinemia was the most frequent diagnosis, followed by SIgAD and CVID; SAD accounted for 5 of 45 humoral PID cases (11.1%). Earlier Pakistani studies reported humoral defects as 21.6% and 28% of broader PID cohorts but did not provide a directly comparable SAD estimate [8,9]. A selected Korean adult antibody-deficiency cohort reported SAD in 23.4% [7]. These differences may reflect age, referral patterns, eligibility criteria, access to vaccine-response testing, and the denominator used. Our 11.1% is the proportion within confirmed humoral PIDs at one referral center and should not be interpreted as population prevalence.

The SAD group had later median onset and diagnosis and a longer median diagnostic delay than the non-SAD group, but none of these comparisons reached the prespecified significance threshold. Accordingly, the findings show directional differences rather than evidence of independent clinical distinctions. Delayed recognition is biologically and clinically plausible because SAD requires functional antibody testing, yet the present data cannot establish the cause of delay [11]. Family history and consanguinity also did not differ significantly; the study was not powered to infer inheritance patterns [12].

Asthma/atopy was recorded in 80.0% of SAD patients and 32.5% of non-SAD patients. The two-sided Fisher exact p value was 0.060, so this result is best described as an imprecise, non-significant difference rather than an association. Prior reports

have described overlap between antibody deficiency and atopic disease [13,14]. Recurrent otitis media was less frequent in SAD than in non-SAD patients in this cohort, whereas respiratory infection was frequent in both groups; neither comparison was significant. These results are compatible with heterogeneous presentations reported in other humoral-PID cohorts [15].

The clearest observed difference was in switched-memory B cells: the SAD mean was 5.0 percentage points lower than the control mean, with $p=0.003$ and a large standardized effect ($d=-1.835$). The 95% CI for d was wide (-3.006 to -0.625), and only five SAD patients were available; therefore, the magnitude should be regarded as preliminary. The naïve B-cell comparison was non-significant ($p=0.208$), and its effect-size CI crossed zero. Reduced switched-memory compartments have been described across predominantly antibody deficiencies [16-18], but the current comparison included healthy controls only and cannot determine whether the finding is specific to SAD rather than shared with CVID or other humoral PIDs.

Several limitations affect interpretation. The THI (n=2) and SAD (n=5) symptom percentages are especially imprecise because of the small diagnosis-specific denominators. The census yielded only five SAD cases, limiting power for clinical comparisons and producing wide effect-size intervals. The single-center referral sample is vulnerable to spectrum and referral bias and does not estimate population prevalence. The dataset did not include genetic results or longitudinal infection, treatment, quality-of-

life, or outcome data. B-cell subsets were available for SAD and controls but not for the other humoral-PID groups. Although post-immunization responses were assessed, PPV-23 was unavailable; reliance on PCV-13 and seven serotypes may affect diagnostic comparability. Multiple exploratory comparisons were made without multiplicity adjustment, so confirmatory studies should prespecify primary outcomes and sample-size assumptions.

Despite these limitations, the study demonstrates a practical local workflow that combines quantitative immunoglobulins, functional pneumococcal antibody testing, and B-cell phenotyping. The data support further prospective, multicenter work with harmonized vaccine-response criteria, complete B-cell panels across diagnostic groups, and an a priori sample-size calculation based on a prespecified primary endpoint. Such studies are needed before clinical cutoffs or prognostic claims can be derived from the observed switched-memory B-cell difference.

CONCLUSION

Agammaglobulinemia was the most frequent humoral PID in this referral cohort, and SAD represented 11.1% of the 45 cases. Clinical differences between SAD and non-SAD groups were not statistically significant. SAD patients had a lower mean switched-memory B-cell percentage than healthy controls, but the estimate was based on five cases and requires confirmation. Functional antibody testing remains central to SAD diagnosis, while B-cell phenotyping may provide complementary characterization rather than a stand-alone diagnostic test.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

Disclosure

None

AUTHORS CONTRIBUTION

Mustajab Alam: Study design, acquisition of data, manuscript drafting, final approval, responsible for every aspect of the research

Hamid Nawaz Tipu: Dermatological assessment and interpretation of cutaneous findings, critical review for important intellectual content, final approval, responsible for every aspect of the research

Raja Kamran Afzal: Analysis and interpretation of data, critical review for important intellectual content,

final approval, responsible for every aspect of the research

Muhammad Hussain: Acquisition of data, manuscript drafting or review for important intellectual content, final approval, responsible for every aspect of the research

Muhammad Zain Ul Abdeen Javed: Acquisition of data, manuscript drafting or review for important intellectual content, final approval, responsible for every aspect of the research

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