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ORIGINAL ARTICLE

## Impact of delayed diagnosis in children with primary antibody deficiencies

Asghar Aghamohammadi<sup>a</sup>, Ahmad Bahrami<sup>a</sup>, Setareh Mamishi<sup>b,\*</sup>,  
Babak Mohammadi<sup>a</sup>, Hassan Abolhassani<sup>a</sup>, Nima Parvaneh<sup>a</sup>,  
Nima Rezaei<sup>a,c,d</sup>

<sup>a</sup> Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

<sup>b</sup> Infectious Disease Research Center, Tehran University of Medical Sciences, Tehran, Iran

<sup>c</sup> Molecular Immunology Research Center, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

<sup>d</sup> Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

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### KEYWORDS

Delay;  
Diagnosis;  
Infection;  
Predominantly antibody  
deficiencies

**Background:** Primary antibody deficiencies (PADs) are heterogeneous group of disorders, characterized by hypogammaglobulinemia and increased susceptibility to recurrent infections. To evaluate the diagnostic delay in Iranian PADs in association with their infections, we scored such manifestations to find an association between such delay and the scoring system.

**Methods:** Forty-eight patients with PADs, who were referred to our center during a 25-year period, were enrolled in this study. Each episode of infection, before making the PADs diagnosis, got a score of 5 or 10 based on the severity of infections.

**Results:** The diagnosis was made with median delay of 34.5 months, when the patients had mean score of  $94.48 \pm 52.89$ . There was a significant direct association between this scoring system and delay diagnosis. The score of 50 was considered as the cutoff point in our patient group. In this score, the suspicions to PADs in more than 90% of patients true positively lead to diagnosis of PADs.

**Conclusion:** Although diagnosis delay significantly decreased over time, PADs still continue to be diagnosed late. Based on the results of this study, the assessment of immune system should be performed in the patients with 50 total score or about 25 score per year.

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\* Corresponding author. Children's Medical Center Hospital, Dr Qarib St, Keshavarz Blvd, Tehran 14194, Iran.  
E-mail address: [smamishi@tums.ac.ir](mailto:smamishi@tums.ac.ir) (S. Mamishi).

## Introduction

Primary immunodeficiency diseases (PIDs) are classified into eight main categories, including (1) combined T- and B-cell immunodeficiencies; (2) predominantly antibody deficiencies; (3) other well-defined immunodeficiency syndromes; (4) diseases of immune dysregulation; (5) congenital defects of phagocyte number, function, or both; (6) defects in innate immunity; (7) autoinflammatory disorders; and (8) complement deficiencies.

Predominantly antibody deficiencies (PADs) are heterogeneous group of disorders, ranging from a severe reduction of all serum immunoglobulin isotypes with the absence of B cells to specific antibody deficiency with normal serum immunoglobulins.<sup>1</sup> PADs are the most common forms of PIDs, which consist of more than half of all PIDs. Among the patients with PADs, common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA), and Hyper-IgM (HIGM) syndromes are the predominant symptomatic diseases.<sup>2–4</sup>

Hypogammaglobulinemia is the main characteristic of the PADs, which prone the patients to bacterial infections. The most common infectious complication in patients with PAD is sinopulmonary infection, caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, and sometimes mycoplasma infections.<sup>2,3,5–7</sup> Patients with PADs also experience gastrointestinal symptoms including chronic diarrhea and malabsorption.<sup>6–10</sup>

Early diagnosis and adequate therapy are the keys to survival and a better quality of life of patients. Regular immunoglobulin replacement therapy reduces serious bacterial infections in the patients with XLA<sup>11,12</sup> and CVID,<sup>13,14</sup> whereas delays in diagnosis and/or inadequate management may lead to permanent organ damage such as bronchiectasis and bronchiolitis obliterans or even death from overwhelming infections.<sup>15–17</sup>

It has been shown that diagnosis of antibody deficiency in patients is associated with considerable delay ranging from 2.5 to 5 years in children and adults,<sup>5–7,18</sup> which is because of lack of the knowledge about PADs among the medical community. A few studies were previously been attempted to score the infectious complications of patients with PADs to find an association between the patients' score and suspicious to such diagnosis.<sup>15,18,19</sup>

To evaluate the diagnostic delay in Iranian PADs in association with their infections, we scored such manifestations to find an association between such delay and the scoring system.

## Patients and methods

### Subjects

Among the patients with PADs, who were referred to Children's Medical Center Hospital, 48 cases were selected as subjects of this study. They have been referred to this main referral center for PIDs in Iran during a 25-year period (1982–2007). The diagnosis of PADs was made based on standard criteria, introduced by the European Society for Immunodeficiencies and Pan-American Group for Immunodeficiency.<sup>20</sup> XLA was confirmed by mutation analysis of bruton tyrosin kinase gene in agammaglobulinemic male

patients with reduced number of B cells (<1%).<sup>9</sup> HIGM was diagnosed by mutation analysis of CD40 ligand (*CD50L*), *CD40*, and activation-induced cytidine deaminase genes in the patients with reduced serum levels of IgG and IgA and normal or elevated IgM level.<sup>21</sup> Mutations in the tumor necrosis factor receptor family member Transmembrane Activator and calcium-modulating cyclophilin ligand Interactor as well as inducible costimulator and *CD19* were also investigated and only the patients without such genetic defects were included in this study.<sup>22</sup> The diagnosis of CVID was made on the patients with decreased serum levels of two or more IgG, IgM, and IgA, and exclusion of other well-defined single gene defects.<sup>1</sup>

### Scoring system

Diagnosis delay is considered as the duration between the age of first episode of infection and diagnosis age. Each episode of infection, before making the PADs diagnosis, got a score of 5 or 10 based on the severity of disease. Score of 10 was considered for the major infections, including pneumonia, meningitis, septic arthritis, osteomyelitis, and severe diarrhea, which need hospitalization (Table 1). Score of 5 was considered for minor out-patients infections, including otitis media, sinusitis, and mild diarrhea.<sup>18</sup>

### Statistical analysis

Data analysis was performed using SPSS statistical software package (version 14.0; SPSS Inc., Chicago, IL, USA). Independent samples *t* test was performed to compare the means between the two groups of patients who were diagnosed before 1997 and during 1997–2007. Linear regression was used to determine the association between delay diagnosis and rate of hospitalization and also delay diagnosis and scoring system. A *p* value of less than 0.05 was considered significant. To evaluate our patients' score, Receiver Operating Characteristic (ROC) curve was used. Sensitivity and specificity for each cutoff point were calculated.

## Results

### Characteristics of patients

In this study, 48 patients (35 male and 13 female) with PADs, aged 6 months to 16 years (median: 5 years), were studied. Among them, 32 patients had CVID (21 male and 11 female), 11 male had XLA, and 5 cases had HIGM (3 male and 2 female). Thirty patients were from consanguineous parents (62.5%). There was positive family history of recurrent infections and early death in 21 families (43.8%).

### Infections complications

All the patients presented with infections in different organs, especially in the respiratory and gastrointestinal systems, before the diagnosis of PAD. Pneumonia was the most common manifestations of these patients, which was seen in 35 patients (73%). Twenty-four cases experienced episode of sinusitis before diagnosis (50%), whereas

**Table 1** The scoring system used in this study

Score 10	Score 5
In-patients severe infections	Out-patients mild infections
Pneumonia	Sinusitis
Septic arthritis	Diarrhea
Meningitis	Otitis media
Osteomyelitis	
Serious upper respiratory infection	

diarrhea and otitis media were reported in 20 (42%) and 16 (33%) patients, respectively. Six patients experienced septic arthritis, three patients with meningitis, and one patient complicated with osteomyelitis.

**Diagnosis delay**

These PAD patients were diagnosed with a mean delay of  $44.58 \pm 38.15$  months (median: 34.5 months, range: 1 month–14 years). The diagnosis delay was less than 3 years in half of these patients, whereas the remaining 24 cases were diagnosed with a delay of more than 3 years.

Comparison of diagnosis delay between two groups of patients who were diagnosed before 1997 (30 cases) and during 1997–2007 (18 cases), indicated that the diagnosis was made significantly earlier in the recent years ( $56.13 \pm 41.16$  vs.  $25.33 \pm 22.49$ ,  $p = 0.002$ ).

**Hospital admission**

Infectious complication led to total of 201 hospital admission during 2,140 months delay of diagnosis. Analysis of

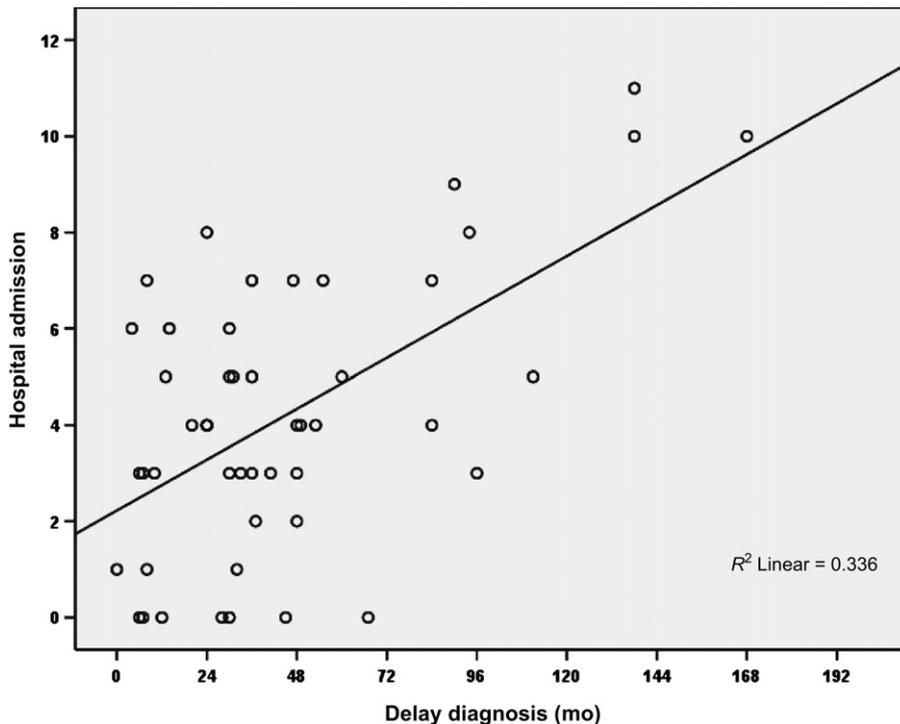
hospitalization per patient before diagnosis indicated that mean hospital admission per patient per year was 2.05. Statistical analysis of these data was complicated by the fact that there was a significantly direct association between delay diagnosis and rate of hospitalization ( $R = 0.579$ ,  $R^2 = 0.336$ ,  $F = 23.24$ ,  $p < 0.001$ ) (Fig. 1).

**Scoring of the infections**

Considering the scoring system, which was explained in the Methods section, the patients had mean score of  $94.48 \pm 52.89$  before the diagnosis was made (median: 80 score, range: 15–275 score). There was a significantly direct association between this scoring system and delay diagnosis ( $R = 0.856$ ,  $R^2 = 0.732$ ,  $F = 125.59$ ,  $p < 0.001$ ) (Fig. 2). Comparison of the scoring of two patient groups, diagnosed before 1997 (30 cases) and after 1997 (18 cases), showed that in the years before 1997, the patients got more scores before diagnosis in comparison to the years after 1997 ( $105.00 \pm 58.44$  vs.  $76.94 \pm 37.26$ ,  $p = 0.048$ ).

**Evaluation of the patients' score**

Figure 3 presents the ROC curve. This procedure is a useful way to evaluate the performance of classification schemes in which there is one variable (scores) with two categories (sensitivity and 1-specificity) by which subjects are classified. The ROC curve for a test that has some use will lie to the left of the diagonal of the graph. Depending on the implications of false positive and false negative results, and the prevalence of the condition, we can choose the optimal cutoff for a test, from this graph. The area under the curve ( $=0.84$ ) represents the probability that the assay result for a randomly chosen positive case will exceed the result for



**Figure 1.** Association between delay diagnosis and hospital admission.

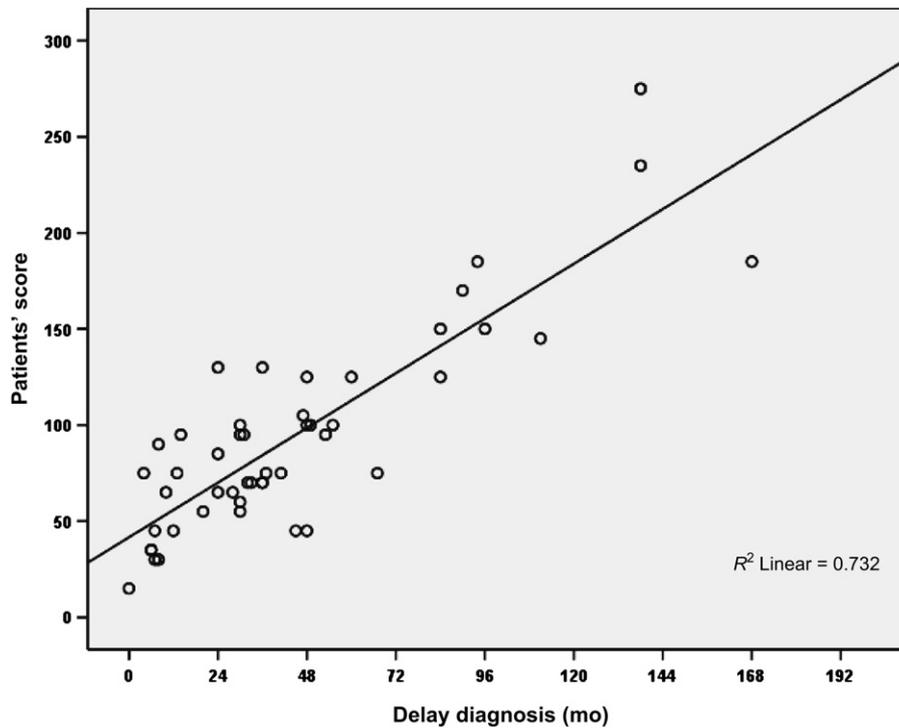
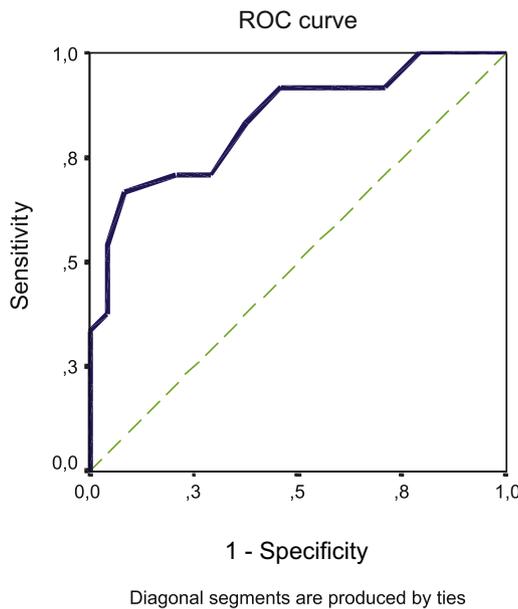


Figure 2. Association between delay diagnosis and patients' score.

a randomly chosen negative case. It is possible to choose a specific cutoff by which patients are classified and estimate the sensitivity and specificity of the scoring system. The related table of Fig. 3 reports the sensitivity and 1-specificity for every possible cutoff for true classification

for the diagnosis of PADs. The sensitivity is the proportion of patients' classification and with scores greater than the cutoff. 1-Specificity is the proportion of patients with less than 3 years in diagnosis whose scores are greater than the cutoff. Cutoff 14 is equivalent to assuming that



Positive if greater than or equal to(a)	Sensitivity	1 - Specificity
140,000	1,000	1,000
225,000	1,000	958
325,000	1,000	875
400,000	1,000	792
500,000	917	708
575,000	917	625
625,000	917	583
675,000	917	458
725,000	833	375
800,000	708	292
875,000	708	250
925,000	708	208
975,000	667	083
1,025,000	542	042
1,150,000	500	042
1,275,000	375	042
1,375,000	333	000
1,475,000	292	000
1,600,000	208	000
1,775,000	167	000
2,100,000	083	000
2,550,000	042	000
2,760,000	000	000

Figure 3. Evaluation of the patients' score. ROC = Receiver operating characteristic.

everyone is positively classified. Cutoff 276 is equivalent to assuming that everyone is negative. Both extremes are unsatisfactory, and the challenge is to select a cutoff that properly balances the needs of sensitivity and specificity. We chose 50 as the cutoff point. In this case sensitivity is 0.9 and 1-specificity is 0.7 (specificity = 0.3). Therefore more than 90% of cases are positively classified correctly (Fig. 3).

We have also analyzed the patients' score per year for the patients, based on the ROC curve and the mean time of delay diagnosis. The mean score per year, which was matched with total score of 50 (sensitivity of 91.7%), was 24.16.

## Discussion

PADs are a heterogeneous group of rare disorders characterized by decreased serum levels of immunoglobulin isotypes and increased susceptibility to infections in different organs, especially in respiratory tract.<sup>1,5-9</sup> Considering the lack of knowledge about PADs among the medical personnel, the diagnosis of the patients is made with some delays.<sup>3,15,18</sup> Diagnostic delay could lead to a lag for providing appropriate treatment, resulting to severe complications and even death in the affected cases.<sup>2,3,17</sup>

In our study, all the patients experienced episodes of infections in different organs, with mean score of 94 before the diagnosis was made. The mean diagnosis delay was more than 3.5 years (45 months), which is similar to previous studies.<sup>6,18</sup> Such delay significantly decreased over time, which could be because of an increase of the physicians' knowledge about such diseases and also better diagnostic tools available in the recent years.<sup>2,3</sup> However, PADs still continue to be diagnosed late and the diagnosis of many cases is made after irreversible end-organ damage.<sup>2,3,18</sup>

All patients with PADs are presented with recurrent infectious complications. Symptoms that were more likely to be helpful in considering the diagnosis of PADs in this study were recurrent infections in the respiratory and gastrointestinal systems. Although sinopulmonary infections and diarrhea are the most common manifestations, septic arthritis, osteomyelitis, and septic meningitis could also be seen in this group of patients.<sup>2,3,23</sup> In fact, early onset recurrent bacterial infections could suggest PADs,<sup>3</sup> which need further evaluation. However, it is not clear when we should suspect to PADs and which patient should be further investigated, because some manifestations are common in healthy subjects as well.<sup>19</sup>

In this study, we used a scoring system, which had previously been introduced by Blore and Haeney.<sup>18</sup> Using the score of 10 for the major infections and the score of 5 for minor infections, our patients had mean score of 95 before the diagnosis was made. Statistical analysis of data indicated this fact that the score of 50 was necessary to make suspicious for PADs, whereas more than 90% of patients are positively classified correctly at this score. However, further evaluation of such scores in non-PADs subjects is also necessary to evaluate the sensitivity and specificity of this score. It should also be modified in different geographical regions.

Considering the patients' score per year, the ROC curve for a test will lie to the right of the diagonal of the graph; so, the ROC curve fails to provide significant values for

sensitivity and specificity of the system. However, the mean score per year of 21 for the patients with delay of more than 3 years, it could be suggested that the patients with either two severe infections per year, or one severe and two minor infections per year could be suspected as patients with PADs, which needs further evaluation.

Based on the results of this study, the assessment of immune system should be performed in the patients with about 25 score per year. It should be noted that Jeffery Modell Foundation (<http://www.jmfworld.com>) suggested 10 warning signs for diagnosis of PIDs. Considering some suggested signs, including eight ear infections, two serious sinus infections, two pneumonias, and two deep-seated infections within 1 year, a mean score of 25 per year is calculated, which is compatible with resulted score in our study.

A diagnosis delay should be considered in the patients with total score of 50, whereas the suspicions to PADs at this score in more than 90% of patients true positively lead to diagnosis of PADs. The selection of one cutoff point scores is necessary for primer survey and balance between usual infections and unusual or over infections. Therefore, our offered scoring and cutoff 50 seems to be completely suitable for logical diagnosis and decreased delay in diagnosis.

Although there are some limitations with such scoring system, it could provide a useful guide for early diagnosis of these patients,<sup>19</sup> whereas early treatment with immunoglobulin replacement therapy can decrease the incidence of recurrent infections and hospitalization in this group of patients.<sup>7,9,12,14,25</sup> Therefore, it is necessary to exclude the PADs diagnosis in the patients with recurrent infections even if they did not reach the cutoff point score, whereas early diagnosis and appropriate management prevent further complications and improve the quality of life of these patients.<sup>2,3,5,24</sup>

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