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CLIN PEDIATR published online 25 August 2011

DOI: 10.1177/0009922811417287

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Clinical Pediatrics
XX(X) 1–5
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DOI: 10.1177/0009922811417287
http://clp.sagepub.com


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Abstract

Literature is lacking on partial IgA deficiency. In this study, the authors propose to describe the clinical manifestations of patients with partial IgA deficiency. *Methods.* The authors conducted a retrospective chart review of 13 patients with partial IgA deficiency followed at the pediatric rheumatology clinic at Robert Wood Johnson Medical School. They looked for the presence of rashes, joint pain, joint swelling, and morning stiffness. The authors also examined charts for a history of frequent infections, allergies, and the presence of elevated antinuclear antibody. *Results.* Eleven out of the 13 patients complained of joint pain, joint swelling, or morning stiffness. Six patients carried a diagnosis of a definitive rheumatic disease. Four patients suffered from frequent infections and 2 patients reported allergies. *Conclusion.* Partial IgA deficiency appears to be associated with rheumatic diseases and complaints of joint pain, joint swelling, and morning stiffness. A larger study is needed to confirm these results.

Keywords

partial IgA deficiency, rheumatic disease

Background

Immunoglobulin A (IgA) is the most common immunoglobulin found in mucosal secretions. After immunoglobulin G (IgG), it is the most abundant immunoglobulin found in the serum.¹ The IgA found in serum is predominantly of subclass A1 and is monomeric in structure. Secretory IgA is composed of both A1 and A2 subclasses and is a dimeric molecule that is attached to a secretory component.² The IgA in mucosal secretions have many functions, including neutralizing bacteria, viruses, and toxins and preventing their entry into cells. The role of serum IgA is less clear, but it is known to be involved in the activation of granulocytes and monocytes.¹ Although techniques exist to measure both serum and secretory IgA levels, in the usual clinical setting, only serum IgA is assessed. Serum IgA levels, as measured by nephelometry, are conventionally reported as being normal when levels lie within 2 standard deviations of the mean.³

Selective IgA deficiency is fairly common in Caucasians and has been reported to affect as many as 1 in 700 individuals of European descent.³ It is the most prevalent of

all of the primary immunodeficiency syndromes. Selective IgA deficiency is defined as having a serum IgA level less than 0.05 g/L.⁴ In contrast, in individuals with partial IgA deficiency, the serum IgA level is greater than 0.05 g/L but less than 2 standard deviations of the mean IgA level for age. A diagnosis of partial IgA deficiency can only be made in individuals older than 4 years of age with normal levels of the other immunoglobulins.⁴ In both selective and partial IgA deficiency, the defect is in B cell differentiation, which leads to a failure of IgA

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bearing B lymphocytes to mature into IgA secreting plasma cells.⁵ In selective IgA deficiency, the arrest in B cell differentiation occurs before class switching whereas in partial IgA deficiency, it seems to occur after class switching.⁶ In a study measuring salivary, urinary, and fecal IgA levels in children with partial and selective or total IgA deficiency, it was found that children with selective IgA deficiency had no salivary or fecal IgA and decreased urinary IgA. Those with partial IgA deficiency had detectable but decreased levels of salivary, fecal, and urinary IgA.⁷

Numerous studies both in the United States and in Europe have demonstrated the presence of selective IgA deficiency in individuals with systemic lupus erythematosus,⁸ rheumatoid arthritis, spondyloarthropathy, and sarcoidosis.⁹ Selective IgA deficiency has also been shown to be associated with celiac disease, upper respiratory tract infections, gastrointestinal tract infections, and malignancies such as gastric and colonic adenocarcinomas.^{3,9-11} However, very little data exist on patients with partial IgA deficiency, and it is not clear whether patients with partial IgA deficiency have an increased incidence of rheumatic disease or infections. The objective of our study is to describe some of the clinical features of patients with partial IgA deficiency seen in our pediatric rheumatology clinic in New Brunswick, New Jersey.

Patients and Methods

We conducted a retrospective chart review of patients with partial IgA deficiency followed at the pediatric rheumatology clinic at University of Medicine and Dentistry of NJ—Robert Wood Johnson Medical School (UMDNJ-RWJMS). These patients were referred to us in order to rule out rheumatic diseases, and the partial IgA deficiency was diagnosed incidentally when laboratory tests were done. Immunoglobulin levels constitute part of the routine work up of patients with complaints that may pertain to a rheumatic disease. We obtained institutional review board approval prior to conducting the study. All the patients included in the study were randomly assigned a number by which they were to be referenced for the purpose of the study. Patient names, birth dates, and number assignments are known only to the authors.

For the purpose of our study, we used age-adjusted values for serum IgA as specified in the 18th edition of *Nelson Textbook of Pediatrics*.¹² For those between 2 and 5 years old, the serum IgA level within 2 standard deviations of the mean ranges from 14 to 159 mg/dL. For those between 6 and 10 years old, it ranges from 33 to 236 mg/dL. For all others, the range is between 70 and 312 mg/dL.¹²

According to the literature, to receive a diagnosis of partial IgA deficiency, an individual must be older than 4 years and have normal levels of all of the other immunoglobulins.⁵ We used age-adjusted means for serum levels of IgG and IgM as well, as specified in the 18th edition of *Nelson Textbook of Pediatrics*.¹²

Based on our criteria for serum IgA levels, 16 patients were initially identified with partial IgA deficiency. After beginning our chart review, we discovered that 1 patient had concomitant IgM deficiency and 2 had IgG deficiency. These 3 patients were therefore excluded from our study. Each of the remaining 13 patients was assigned a number between 1 and 13 by which they were referenced for the purposes of the study. Their charts were reviewed for the presence of joint pain, joint swelling, morning stiffness, and rash. We were also interested in a history of allergies, recurrent infections, tonsillectomy and/or adenoidectomy. Descriptive analysis was performed using SPSS version 16 for Windows (IBM, Chicago, IL).

Results

The 13 patients were between 11 and 18 years old. Six patients were male. Of the 13 patients, 10 patients identified themselves as white/Caucasians and 2 patients identified themselves as black/African American. Racial information for one patient was not available. Serum IgA levels of the patients throughout all age groups ranged from 10 to 65 mg/dL. Serum IgA, IgG, and IgM levels for each of the patients are provided in Table 1. Mean serum IgA, IgG, and IgM levels for our patients with standard deviations are provided in Table 2.

A total of 11 patients had at least one of the following complaints: joint pain, joint swelling, and morning stiffness. Eight patients (numbers 1, 2, 3, 5, 6, 10, 11, and 13) reported joint pains. Of these, 6 patients (numbers 1, 2, 6, 10, 11, and 13) had multiple joints involved. Five patients (numbers 6, 10, 11, 12, and 13) reported joint swelling. Seven patients (numbers 1, 5, 6, 7, 8, 11, and 13) complained of morning stiffness. Only patients 1 and 4 reported a rash. Patient 1 had a psoriasis-like rash on the extremities and patient 4 had a malar rash.

Six patients carried one of the following diagnoses: spondyloarthropathy (numbers 2, 6, and 8), inflammatory arthropathy (number 11), Sjogren's disease (number 13), and Raynaud's phenomenon (number 10). Four patients (numbers 1, 3, 9, and 13) had a positive antinuclear antibody, with titers ranging from 1:80 to 1:320.

Four patients (numbers 2, 10, 11, and 13) reported a history of recurrent infections. Patients 2 and 11 had recurrent otitis, patients 10 and 11 had recurrent sinusitis, and patient 13 suffered from frequent upper

Table 1. Serum Immunoglobulin Levels in Patients With Partial IgA Deficiency^a

Patient No.	Age (Years)	Serum IgA (70-312 mg/dL)	Serum IgG (639-1349 mg/dL)	Serum IgM (56-352 mg/dL)
1	12	22	838	97
2	15	63	822	143
3	11	65	1006	179
4	13	38	671	80
5	17	46	814	164
6	18	13	1350	107
7	12	56	1388	80
8	15	10	1514	175
9	12	50	960	122
10	14	12	1610	103
11	15	51	727	103
12	14	54	1460	95
13	11	23	1228	85

^aThe ages and serum immunoglobulin levels of the patients included in the study are listed. Normal ranges for serum IgA, IgG, and IgM are indicated in parentheses.

Table 2. Mean Serum Immunoglobulin Levels Stratified by Age^a

Variable	Mean $\pm$ SD		
	11-12 Years (n = 5)	13-15 Years (n = 6)	16-18 Years (n = 2)
IgA (70-312 mg/dL)	43 $\pm$ 20	38 $\pm$ 22	30 $\pm$ 2
IgG (639-1349 mg/dL)	1084 $\pm$ 221	1134 $\pm$ 437	1082 $\pm$ 379
IgM (56-352 mg/dL)	112 $\pm$ 41	116 $\pm$ 35	135 $\pm$ 40

^aMean serum IgA, IgG and IgM levels in mg/dL for the patients in the study, along with standard deviation. Normal ranges for serum IgA, IgG, and IgM are indicated in parentheses.

respiratory infections. Only patients 9 and 11 reported allergies. Patient 9 had food allergies whereas Patient 11 had seasonal allergies. Patient 12 suffered from eczema. Finally, only 1 out of the 13 patients (patient 2) had undergone a tonsillectomy and adenoidectomy.

Discussion

IgA deficiency is a highly prevalent disease entity in the United States. Individuals with IgA deficiency may be completely asymptomatic or may have associated recurrent sinopulmonary and/or gastrointestinal infections, or autoimmune diseases such as celiac disease or rheumatoid arthritis.³

In our study of 13 children with partial IgA deficiency, 23% had associated spondyloarthropathy. One patient each carried an associated diagnosis of Sjogren's disease, juvenile rheumatoid arthritis, Raynaud's syndrome, or inflammatory arthropathy.

Generally, 7% of individuals with IgA deficiency are reported to have coexisting juvenile rheumatoid arthritis and systemic lupus erythematosus.³ In one study,

selective IgA deficiency was associated with 5.2% of children with systemic lupus erythematosus.⁸ In the same study, selective IgA deficiency was associated with juvenile rheumatoid arthritis in 3.44%, dermatomyositis in 7.31%, systemic scleroderma in 6.6%, and with mixed connective tissue disease in 7.14% of the children in the study.⁸ Asymptomatic adults with selective and partial IgA deficiency followed over a 20-year period were discovered to have increased incidence of rheumatoid arthritis, sarcoidosis, and spondyloarthropathies as compared with individuals with normal IgA levels.⁹

The majority of our patients also reported experiencing symptoms such as joint pain or joint stiffness. Specifically, 73% of our patients reported joint pains, and 75% of these patients complained of pain in multiple joints. Another 64% suffered from morning stiffness. In all, 45% of the patients we studied mentioned having swollen joints. Although numerous studies have demonstrated an association between IgA deficiency and rheumatic diseases, to our knowledge, no studies have addressed the presence of joint pain, joint swelling, and morning stiffness in individuals with partial IgA deficiency. There

are many etiologies for joint pain and even joint swelling, including injury, overuse, and reactive or septic arthritis. Morning stiffness, on the other hand, is more specific for the presence of a rheumatic disease. Three out of the 13 patients suffered from all 3 symptoms and carried one or more rheumatic disease diagnoses. Two of these 3 patients (numbers 11 and 13) also reported a history of recurrent infections. In addition, patient 11 reported a history of seasonal allergies.

In total, 31% of our patients reported a history of recurrent infections. These were mostly sinus infections and otitis. Unfortunately, the details of the number of annual episodes of infection were not available. Individuals with IgA deficiency have been observed to be more prone to sinopulmonary infections with *Haemophilis influenzae* and *Streptococcus pneumoniae*.¹⁰ In a study of 37 patients with selective IgA deficiency, Aghamohammadi et al⁴ found recurrent infections in 73% initially and 94% at follow-up. Sinusitis was the most common and otitis was the second most common infection seen in this group.⁴ Janzi et al¹¹ studied 14 children with selective IgA deficiency and 328 children with partial IgA deficiency and found a significantly increased incidence of pseudocroup in the selective IgA-deficient children compared with the partial IgA-deficient and non-IgA-deficient children.¹¹ In children with partial IgA deficiency, otitis was still the most common infection with 22% affected.¹¹ However, there was no difference in the incidence of otitis or any other infection in the partial IgA-deficient group as compared with the non-IgA-deficient group.¹¹

Overall, 23% of our patients complained of having multiple allergies. These included food allergies, seasonal allergies, and eczema. There is an inconsistent association of allergies with IgA deficiency. Some studies report a higher incidence of allergic symptoms in individuals with IgA deficiency as compared with the general population.^{4,10} Asthma, eczema, and food allergies were some of the more common entities associated with IgA deficiency in these individuals.^{4,10} A prior study in patients with selective and partial IgA deficiency reported an increased incidence of food hypersensitivity in the selective IgA-deficient group as compared with the non-IgA-deficient group.¹¹ No differences in associated allergies were, however, reported in the partial IgA-deficient group. No association between asthma or eczema and IgA deficiency was also found in this study.¹¹

One of our patients had a malar rash whereas another complained of a psoriasis-like rash over his extremities. Samolitis et al¹³ report 2 individuals with partial IgA deficiency with a pruritic, papulovesicular rash on the extensor surfaces of their upper and lower extremities that was later diagnosed as dermatitis herpetiformis. Multiple case reports document a

lipoatrophic rash in the lower abdomen¹⁴ or a centrifugally spreading, lipoatrophic, bluish erythematous rash in the lower abdomen¹⁵ in children with partial IgA deficiency. Rashes can also be seen in many rheumatic conditions. A malar rash is classically seen in individuals with systemic lupus erythematosus. Interestingly, neither of our patients with a rash had a rheumatic diagnosis.

Our study was limited by its retrospective nature and small sample size. Unfortunately, we do not have the exact percentage of patients with partial IgA deficiency in our clinic. Since there is no ICD (International Classification of Diseases) code for partial IgA deficiency, it is difficult to obtain the total number of patients with this diagnosis. As stated previously, the fact that our patients were being followed at the pediatric rheumatology clinic for various rheumatic complaints and diagnoses represents a selection bias, which could explain the higher rates of spondyloarthropathy and other rheumatic complaints seen in our patients than previously reported. We did not perform additional statistical analysis because of the relatively small sample size.

Conclusion

There is a paucity of data on clinical symptoms associated with partial IgA deficiency. We observe some very interesting associations of rheumatic complaints with partial IgA deficiency in patients in our study. However, our sample size is too small to make any definitive conclusions. Larger studies will be required to examine the association of partial IgA deficiency with rheumatic complaints and disorders. Children with partial IgA deficiency will also need to be compared with healthy children to determine how clinical features differ between the 2 groups. Finally, long-term follow-up of children with partial IgA deficiency is critical to understand the various diseases this population is predisposed to.

Authors' Note

Suneetha Chamathi did this work while she was working in our department of Pediatrics, UMDNJ-RWJMS as a volunteer.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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