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Coincidence of selective immunoglobulin A deficiency in juvenile idiopathic arthritis – a series of three cases

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Abstract

Immunoglobulin A (IgA) deficiency is the most common primary immunodeficiency in humans, with incidence depending on ethnic background and the highest frequency in Caucasians. Selective IgA deficiency may have an asymptomatic course and constitute a random laboratory finding with no clinical manifestation. There is, however, a group of patients with increased incidence of recurrent upper respiratory tract infections, allergies, asthma, atopic dermatitis and other pathologies connected with IgA deficiency. This group of patients often needs broad-spectrum antibiotic therapy with maximum doses and extended time of treatment as there is no causal treatment for IgA deficiency. An association between IgA deficiency and autoimmune diseases, such as juvenile idiopathic arthritis, has been proved before. Nonetheless, the frequency of co-occurrence of these disorders in an individual as well as the way immunodeficiency may influence the course of juvenile idiopathic arthritis is still undefined, with limited literature on this topic. This article presents case reports of three pediatric patients with confirmed co-occurrence of IgA deficiency and oligoarticular juvenile idiopathic arthritis.

Key words: *selective IgA deficiency, SIgAD, juvenile idiopathic arthritis, JIA.*

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Introduction

Selective immunoglobulin A (IgA) deficiency (SIgAD) is the most common primary immunodeficiency, which occurs in approximately 1 out of 600 Caucasian individuals [1]. This disorder is defined by the European Society for Immunodeficiencies as a serum IgA level less than 7 mg/dl (0.07 g/l) with normal IgG and IgM serum levels in patients over 4 years old in whom other causes of hypogammaglobulinemia have been excluded [2]. Many individuals with SIgAD are asymptomatic; however, there is an increased incidence of upper respiratory tract infections, allergies, autoimmune diseases, and malignancies among these patients. A plethora of autoimmune associations have been reported, including autoimmune thyroiditis, idiopathic thrombocytopenic purpura, hemolytic anemia, sclerosing cholangitis, celiac disease, psoriasis, inflammatory bowel disease, systemic lupus erythematosus, and others [3]. There are several suggested mechanisms of autoimmunity in SIgAD; however, none of these hypotheses are definitive [4]. Another autoimmune disorder of positive association with IgAD is juvenile idiopathic arthritis (JIA) [5]. According to the International League of Associations for Rheumatology, JIA comprises a heterogeneous group of several disease subtypes that are characterized by the onset of arthritis before the age of 16 years and with symptoms lasting for at least 6 weeks [6, 7]. The pathogenesis of JIA involves a varying combination of both autoimmune and environmental factors; the details of this process remain unclear. The association between SIgAD and JIA is supported by nine studies in which prevalence of SIgAD among children with JIA was examined. Children with SIgAD who had JIA were found to be in the range of 1% to 4.35% with a weighted average of 2.7%. In one study of 2100 children, 0.76% with known SIgAD had JIA, compared to 0.009% within the control group [4]. Reports of the mutual impact of coexisting SIgAD and JIA, and influences on the course of both disorders, are limited. Some studies suggest higher compensatory IgM serum levels in patients with additional autoimmunity and lower IgG levels in patients with or without additional autoimmunity, although clinical influences are yet to be described [8].

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Herein, we present a series of three cases of coexisting SIgAD and JIA. An analysis of the course of each case is reported in order to better understand and describe the clinical implications of both disorders. We also would like to underline the importance of including checking of total IgA concentration during diagnosis of JIA and other autoimmune diseases in pediatric patients.

Case reports

Case A

Patient A is a 7-year-old female with no family history of autoimmune disease. Beginning at age 4, she suffered from monoarthritis of the right knee joint with enlargement of the right knee, tissue swelling, effusion, and contraction of the joint with an antalgic gait. Test results at this time showed a normal blood count, normal erythrocyte sedimentation rate (ESR) and negative anti-cyclic citrullinated peptide (anti-CCP) with antibodies against *Mycoplasma pneumoniae*, Lyme *Borrelia* and *Yersinia*. IgA was not detected (0.00 g/l, norm: 0.08-1.49 g/l), with a slightly elevated IgG level (12.60 g/l, norm: 4.68-11.05 g/l). An ultrasound scan of the right knee joint showed swelling and effusion of the synovial membrane with features of increased vascularization. Synovial fluid was cloudy and yellow with 2860 mg% protein and positive Rivalta's test. For treatment, nonsteroidal anti-inflammatory drugs were administered, which led to a slight improvement. After eliminating the risk of reactive arthritis, the patient was given intraarticular betamethasone.

At age 5 she was diagnosed with JIA and treated with methotrexate with good tolerance. Her Juvenile Arthritis Disease Activity Score (JADAS)-71 score was 22. Tests showed microcytic anemia with iron deficiency (HGB = 10.9 g%, norm: 11.5-14.5 g%; HCT = 34.3%, norm: 35-45%; MCH = 25.0 pg, norm: 26-33 pg; MCHC = 31.7 g%, norm: 32.0-37.0 g%; Fe = 18 µg%, norm: 50-120 µg%) and normal ESR. C3 and C4 were within normal limits. Other abnormalities in serum immunoglobulin were discovered: undetected IgA (0.00 g/l, norm: 0.25-1.38 g/l) with slightly elevated IgG (13.40 g/l, norm: 5.53-12.32 g/l). Rheumatoid factor (RF) was negative and antinuclear antibodies ANA1 were not found while ANA3 showed a high positive result for DFS70 (+++). For treatment, the patient was administered repetitive intraarticular injections of betamethasone and methylprednisolone. Methotrexate was replaced with sulfasalazine therapy at the age of 7.

Case B

Patient B is a 19-year-old female diagnosed with juvenile idiopathic arthritis at the age of 12 who was treated with methotrexate. The predominant clinical signs were enlargement of the left knee joint and mild synovial hypertrophy (3 mm) of the right knee in ultrasound. Tests did not detect any abnormalities apart from an IgA level of 0.00 g/l recurring in further tests. Her JADAS-71 score was 10.

At age 16, the patient presented exacerbation of disease with enlargement of the left knee joint and both radiocarpal joints. An ultrasound scan of the right radiocarpal joint showed synovial hypertrophy with no sign of increased vascularization. Despite an increased dose of methotrexate, inflammation in the affected joints continued, causing pain, swelling and a restricted range of motion in the right radiocarpal joint with swelling with limited effusion in both knee joints. The patient was given an intraarticular injection of betamethasone.

One year later, the patient was admitted to the clinic with swelling and effusion of the knee joints, ankle joints, subtalar joints, right metatarsus and right elbow. Tests showed a normal blood count, normal ESR and negative anti-CCP and antibodies against *Yersinia*, *Chlamydia trachomatis*, *Borrelia*, cytomegalovirus (CMV), hepatitis B virus (HBV) and hepatitis C virus (HCV). C3 and C4 were within normal limits. IgA remained undetected (0.00 g/l, norm: 0.70-4.00 g/l) and levels of IgM and IgG were normal. Her JADAS-71 score was 21. RF was negative. Because of the increased number of affected joints, the diagnosis was changed to extended oligoarticular JIA. The patient qualified for biological treatment with continuation of methotrexate and sulfasalazine.

Case C

Patient C is a 5-year-old girl with a family history of psoriatic arthritis (father). She was diagnosed with JIA at the age of 2 with predominant clinical indications of antalgic gait and morning stiffness, with no prior infection or injury. The patient presented swelling, effusion and restriction of mobility of the knee joints, swelling of the proximal interphalangeal joint of the left index finger, and swelling of the interphalangeal joint of the left hallux. Tests showed a normal blood count and elevated ESR (39 mm/h, norm: 3-15 mm/h). Antibodies against *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, Lyme *Borrelia* and *Yersinia* were negative as well as anti-CCP. IgA was not detected (0.00 g/l, norm: 0.17-1.00 g/l) while IgM and IgG were within normal limits. Her JADAS-71 score was 22. An ultrasound scan of the affected joints showed significant swelling of the synovial membrane in the left knee joint with accompanying features of increased vascularization. Similar findings were detected in the interphalangeal joint of the left hallux and the metatarsophalangeal joint. A knee joint puncture under general anesthesia was performed with subsequent injection of betamethasone. For further treatment, methotrexate and prednisone were administered. Further diagnostics showed a normal blood count and normal ESR. IgA remained undetected (0.00 g/l) and IgG was slightly elevated (11.30 g/l, norm: 4.08-10.20 g/l). RF, ANA1 and ANA3 were negative. X-ray

of the lower limbs at age of 5 showed a leg length discrepancy, with the left limb being 8 mm shorter than the right limb and the right ala of the ilium being 18 mm higher than the left.

Discussion

Immunoglobulin A is the second most dominant antibody isotype in the blood circulation following IgG. IgA has a monomeric-circulating form and dimeric-secretory form which can be found in mucosal secretions of the respiratory, intestinal, and genitourinary systems [9]. IgA deficiency is the most common primary immunodeficiency. The pathogenesis of SIgAD is not clear. There are studies linking SIgAD to heavy chain gene deletions involving various segments on chromosome 14, with abnormalities in the cytokine network such as a lack of interleukin (IL)-4, IL-6, IL-7, IL-10, transforming growth factor β (TGF-β), and IL-21 and in the MHC region, in particular, HLA-B8, DR3, and DQ2 [9-11]. In a majority of cases (85-95%), IgAD is a permanent deficiency with no clinical manifestations. There is no causal treatment for IgAD yet, although recurrent infections may lead to broad-spectrum antibiotic therapy that is introduced in the very first phase of infection with maximum doses and extended treatment times [12].

Despite the relatively low possibility of autoimmunization in IgAD patients, there is a confirmed association between these two pathologies. According to a multicenter study of 2030 individuals with JIA, the total prevalence of IgAD was 1 : 37, which is significantly higher than the population prevalence [13]. There are only a few publications concerning the relationship between IgA deficiency and JIA [6, 14]. The case studies available consider the topic in terms of aberrations and do not address juvenile oligoarticular arthritis itself [15, 16].

There are independent biological and clinical predictive factors of severe oligoarticular JIA which are useful for identification of high-risk patients who may benefit from early and aggressive treatment [10]. To assess the current activity of the disease, the JADAS is commonly used. It consists of an evaluation of four measures: the physician's global assessment of disease activity, the parent/guardian or patient's global assessment of overall wellbeing, the number of joints with active arthritis and the ESR level. Depending on the number of joints being assessed, there is the JADAS-71 complete joint count evaluation, JADAS-27 and JADAS-10 with a reduced number of joint analyses (27 and 10 respectively).

The case reports presented here show 3 patients diagnosed with JIA and SIgAD between the years 2013 and 2017. All three patients were female, having neither allergies nor a history of recurrent infections. This leads to their classification as asymptomatic cases of SIgAD with IgA deficiency being an unanticipated finding. The main impetus for diagnostics in these three patients was the presence of clinical symptoms suggesting arthritis of the knee joint. Only patient C had a family history of autoimmune disease, which was paternal psoriatic arthritis. This patient, at 2 years of age, was also the youngest to present the first symptoms of arthritis.

The early onset of monoarthritis in patients A and C is compatible with general JIA data as the age of onset in oligoarticular arthritis is estimated to be between 1 and 5 years of age with a peak at 3 years of age [17]. The primary involvement of the knee joints in patients A, B and C agrees with the percentage data of the most common manifestation of JIA, as 50% of cases present knee joint arthritis [18]. In all three patients, test results for RF and anti-CCP were negative. Pathogen-induced arthritis was excluded and C3 and C4 were within normal limits. ANA3 showed a high positive result for DFS70 (+++) only in case A. The listed diagnostic tests are useful for assessment of disease activity as the presence of the immune complexes anti-CCP, RF and the activity of the complement system positively correlate with the severity of JIA [19]. Uveitis, the main disability factor in patients, was not described in any case [20].

A comparison of the age of onset, JIA diagnosis with JADAS-71 score, and the first IgA deficiency detected is presented in Table 1. The short time period from diagnosis to detection of IgA deficiency suggests that earlier coexistence of the disorder is more probable than it being a side effect of therapy; however, cases of acquired IgA deficiency after immunosuppressive therapy have been reported [21].

The IgA levels remained undetected in repeated tests for all three patients. Only in patient A was the IgA deficiency accompanied by slightly elevated IgG, which is not typical for SIgAD. In these described cases, detection of IgA deficiency was an unexpected result of laboratory tests and occurred parallel to the JIA diagnosis. In tracking the course

Table 1. Age of onset, diagnosis and IgAD detection and JADAS-71 score of described patients

Patients	Age of arthritis onset	Age of JIA diagnosis	JADAS-71 score at diagnosis	Age of IgA deficiency (0.00 g/l) in laboratory studies
Patient A	4 $^{7/12}$	5	22	4 $^{10/12}$
Patient B	12	12 $^{6/12}$	10 21*	12 $^{6/12}$
Patient C	2 $^{8/12}$	3	16	2 $^{10/12}$

** Evaluation repeated at time of diagnosis of extended oligoarticular JIA, JIA – juvenile idiopathic arthritis*

of the disease in all three cases, it seems that SIgAD did not significantly affect their clinical status, as the complications most commonly seen among IgA deficient patients such as allergies, asthma, atopic dermatitis, otitis media, urinary tract infections, gastrointestinal infections, and malabsorption did not occur over the course of this study.

The therapy introduced focused on juvenile idiopathic arthritis and consisted of methotrexate in adjusted doses, intraarticular injections of glucocorticosteroids, and non-steroidal anti-inflammatory drugs accordingly. In response to the disease course of patient A, the medication was changed from methotrexate to sulfasalazine. Patient C started qualification for a biological treatment program due to the expansion of arthritis and a change in diagnosis to extended oligoarticular JIA at the age of 17, 5 years after the initial diagnosis. Patients A, B, and C are still undergoing therapy.

Conclusions

This paper presents 3 clinical cases of JIA and SIgAD. All three patients were diagnosed in the same regional hospital between the years 2013 and 2017. Both diseases are described in the literature as frequent, with prevalence of 2.6-13.9 per 100,000 for JIA and 1 : 600 (Caucasians) for SIgAD. However, the number of studies concerning the co-occurrence of these diseases is limited and the majority focus on demonstrating the positive correlation between the general prevalence of autoimmune disorders and immunoglobulin deficiency. There are not many publications presenting the possible clinical implications of the coexistence of these disorders, including possible exacerbations of autoimmune disease such as JIA. In the cases presented here, it seems that the deficiency did not significantly affect the course of the autoimmune disease; however, due to the case-report nature of this work, it is difficult to form general conclusions. The fact that the patients did not present recurrent infections or other symptoms of primary immunodeficiency is very important when serologic tests based on specific IgA are used in differential diagnosis, e.g. checking for *Mycoplasma* or *Yersinia* infections to exclude reactive arthritis or during checking for celiac disease. Without previous knowledge about IgA deficiency many false negative results could be taken into consideration. The occurrence of 3 patients with JIA accompanied by SIgAD in one clinical center suggests that the incidence of this clinical combination might not be rare, which makes this article an attempt to inspire research activity and further analysis.

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