









ACCESO  ABIERTO

Selective IgA deficiency, juvenile idiopathic arthritis and anterior uveitis in a Costa Rican child. Coincidental diseases?. Case report and literature review

Deficiencia Selectiva de IgA, artritis idiopática juvenil y uveítis anterior en una niña costarricense. ¿Enfermedades coincidentales?. Reporte de caso y revisión de literatura

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ABSTRACT

Background: selective IgA deficiency is the most frequent primary immunodeficiency worldwide. Patients are usually asymptomatic. However, those cases with symptoms develop recurrent infections and increased risk of autoimmune and malignant diseases. On the other hand, rheumatic disorders are uncommon during childhood with juvenile idiopathic arthritis as the most common one.

Case Presentation: we present the case of a female patient, who developed oligoarticular juvenile idiopathic arthritis at age 7 years. After the diagnosis, she developed acute anterior uveitis. During the initial immunological evaluation, the diagnosis of selective IgA deficiency was confirmed. A work-up for immunodeficiency demonstrated a normal T cell compartment. B cell subpopulations showed normal memory B lymphocytes, absence of transitional B cells, and an increase in the CD21^{low} unique subset.

Conclusions: at the beginning of any rheumatological evaluation, the physician should request immunoglobulins levels, in order to detect possible primary antibodies deficiencies.

Keywords: IgA Deficiency; Juvenile Idiopathic Arthritis; Uveitis; Autoimmunity; Immunoglobulin A.

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RESUMEN

Antecedentes: la deficiencia selectiva de IgA es la inmunodeficiencia primaria más frecuente alrededor del mundo. Usualmente quienes la sufren son asintomáticos. Los casos sintomáticos se caracterizan por infecciones recurrentes, riesgo mayor de enfermedades autoinmunes y/o neoplasias. Por otra parte, las enfermedades reumáticas en la infancia son infrecuentes, siendo la artritis idiopática juvenil la más común.

Presentación del Caso: se presenta el caso de una paciente femenina que desarrolló artritis idiopática juvenil oligoarticular a los 7 años de edad. Posterior al diagnóstico, la paciente presentó uveítis anterior aguda. Posterior a la evaluación inmune inicial, se diagnosticó deficiencia selectiva de IgA. Los estudios realizados para inmunodeficiencia documentaron un fenotipo de célula T normal. El fenotipo de células B evidenció un perfil normal de linfocitos B de memoria, ausencia de linfocitos B transicionales y un aumento en la población B CD21^{low}.

Conclusiones: al inicio de cualquier valoración reumatológica, los médicos deben solicitar niveles de inmunoglobulinas, con el fin de detectar posibles inmunodeficiencias primarias de anticuerpos.

Palabras Clave: Deficiencia de IgA; Artritis reumatoide juvenil idiopática; uveítis; autoinmunidad; inmunoglobulina A.

Abbreviations: SIgAD IgA selective deficiency; PID Primary Immunodeficiency; JIA Juvenile Idiopathic Arthritis; ANA Antinuclear Antibody; HLA Human Histocompatibility Antigen, ILAR International League of Associations of Rheumatology.

BACKGROUND

Selective IgA deficiency (SIgAD) was first described in patients with Ataxia Telangiectasia (1); however, it was later described as a selective humoral deficit with no known genetic cause so far. SIgAD is the most common primary immunodeficiency (PID) in the world that occurs in 1:300-1:700 individuals (2). The clinical spectrum ranges from asymptomatic to symptomatic patients. Those symptomatic cases develop infections mainly of the mucous membranes, allergic disease, autoimmune diseases, and malignant neoplasms in some cases; however, fortunately, asymptomatic cases of SIgAD are the most frequent (3). The diagnostic criteria for SIgAD consist of serum IgA levels <7 mg/dL in patients >4 years of age, along with normal IgG and IgM levels, exclusion of other causes

of hypogammaglobulinemia, normal IgG titers to vaccine antigens, and exclusion of T cell defects (4). On the other hand, Juvenile Idiopathic Arthritis (JIA) is a heterogeneous condition that represents the most frequent rheumatic disease in pediatrics. It is characterized by chronic arthritis not otherwise explained in patients under 16 years of age. JIA is classified according to ILAR criteria into 7 clinical entities: persistent or extended oligoarthritis, rheumatoid factor positive polyarthritis, rheumatoid factor negative polyarthritis, enthesitis related arthritis, psoriatic arthritis, systemic arthritis, and undifferentiated arthritis (4, 5).

Uveitis is a clinically inflammatory intraocular entity. Chronic anterior uveitis is a frequent extra-articular manifestation of JIA. It predominantly affects the iris and ciliary body.

Patients with oligoarticular JIA are at high risk to have uveitis, predominantly with antinuclear antibodies positive (6).

The prevalence of JIA-associated uveitis in Costa Rica is low and has been estimated to 3.2% (7). Overall, the global estimated prevalence of uveitis in patients with known JIA, range from 11.6% to 30% (8)

The purpose of this report is to present a case of a patient with oligoarticular JIA and anterior uveitis associated with SIgAD. Literature documenting the association of this primary humoral immunodeficiency with JIA is reviewed.

CASE PRESENTATION

A 7-year-old female, with no previous relevant perinatal medical history, and no parental consanguinity; presented to our department after twelve weeks of active arthritis and limited range of motion of the right knee and ankle, with morning stiffness of 2 hours. No clinical findings suggesting systemic disease were documented. There was no clinical characteristics of enthesitis, psoriasis, oral ulcers nor inflammatory bowel disease. On physical examination, joint effusion and synovitis were found.

Laboratory tests showed erythrocyte sedimentation rate of 35 mm/hr, thrombocytosis, normochromic anemia, HLA-B27 negative, and normal complement levels. The ANA immunofluorescence test was negative. The diagnosis of oligoarticular JIA was established based on the ILAR criteria (4).

The initial immunological assessment documented normal serum IgG, IgM, and age-appropriate IgG subclasses. Non-detectable IgA, was determined three times. Normal vaccine-specific antibodies

were found. Therefore, SIgAD, was diagnosed concomitant to JIA; no infections or allergic conditions were reported, and celiac disease was ruled out.

The lymphocyte subpopulations of the patient are shown in table 1. A normal age distribution of total B cells, NK cells and T cells was found. The B cell compartment showed a slight decrease in naive B cells ($CD20^+CD10^-CD27^-IgM^+$), normal memory B cell levels, absence of transitional B cells and plasmocytes, and an increase in the B cell compartment $CD21^{low}CD38^{low}$ (Figure 1).

She was treated with weekly oral methotrexate (10 mg/m²), daily prednisone (0.4 mg/Kg) for 4 weeks and folic acid (1mg/d). The patient had improvement of the joint manifestations and decrease in the inflammatory parameters. Eight weeks after starting the treatment she had pain and a red eye. Acute anterior uveitis of the right eye was found and treated with topical ophthalmic steroid, oral prednisone and methotrexate dose was increased (15 mg/m²). Due to gastric intolerance this drug was changed to subcutaneous application.

After 15 months of treatment and remission of arthritis and uveitis, an attempt to interrupt treatment was made; however, the patient presented relapse of arthritis. Therefore, the same treatment was restarted, which remains to this day.

Currently, the patient is in remission of her arthritis and uveitis; last ophthalmological evaluation with visual acuity 20/20 in both eyes, slit lamp right eye with clear corneas, absence of Tyndall's phenomenon, clear crystalline with anterior pigment. There is presence of residual posterior synechiae. She remains free of recurrent infections, allergic manifestations or neoplasia.

Table 1. Immunodiagnostic values, total lymphocytes and B cells subpopulations of the patient*

Test	Measurement in mg/dL	Normal range for age mg/dL ²²⁻²⁴ .
IgA	0	33-202
IgM	107	48-207
Total IgG	900	633-1280
IgG1	450	350-910
IgG2	169	85-330
IgG3	55	20-100
IgG4	98	3-158
Anti-diphtheria toxoid IgG	Positive	-
Anti-tetanus toxoid IgG	Positive	-
Total lymphocyte count	2.7 (10 ³ /uL)	2.28-3.82 (10 ³ /uL)
Lymphocyte subpopulation of the patient		
Cells	Percentages	Age-matched reference values
CD3 ⁺ T cells	75	55-97
CD3 ⁺ /CD4 ⁺ T cells	47 (1272/uL)	26-61
CD3 ⁺ /CD8 ⁺ T cells	16(433/uL)	13-47
CD56 ⁺ NK cells	7	3-31
CD19 ⁺ B cells ^a	13	12-33
CD20 ⁺ CD10 ⁻ CD27 ⁻ IgM ⁺ naive B cells ^b	54	69-80
CD20 ⁺ CD10 ⁺ CD27 ⁻ transitional/immature B cells ^b	0	4.5-9.2
CD19 ⁺ CD20 ⁺ CD27 ⁺ memory B cells ^{b,c}	32 % (113/uL)	64-282/uL absolute count
CD20 ⁺ CD27 ⁺ IgM ⁻ switched memory B cells ^b	8	5-12
CD21 ^{low} CD38 ^{low} unique subset ^b	5	0.9-3
CD24 ⁻ CD38 ⁺⁺ plasmacytes ^b	0	1-3.4

*Peripheral blood analysis, ^a of total lymphocytes, ^b%Of total CD19⁺ cells, ^cTotal memory B cells reported in absolute value

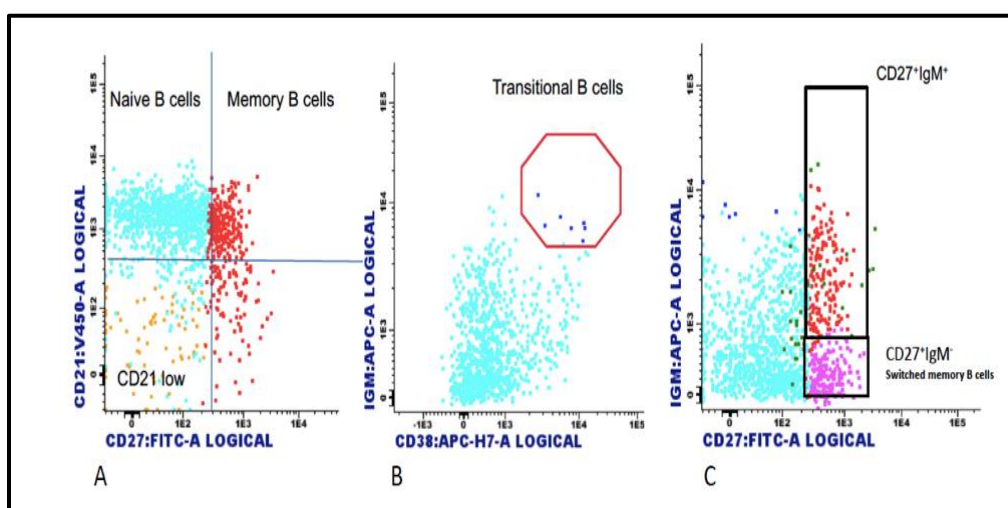


Figure 1. B cells compartment of the patient / **A.** Slightly decreased naive B cells and normal memory B cells for age. CD21^{low} unique subset increased for age / **B.** Absence of transitional B cells / **C.** Normal memory B cells CD27⁺IgM⁺ and switched memory B cells CD27⁺IgM⁻ for age.

DISCUSSION

Various autoimmune diseases have been described as secondary to SIgAD. This selective humoral PID has been associated with autoimmune diseases in 25-30% of patients (9), depending on the population cohorts studied. To date, the etiology of autoimmune diseases in SIgAD is unknown. Some hypotheses are the presence of certain HLA alleles, which predispose to both autoimmune diseases and SIgAD, as is the case of the presence of HLA-A1, B8, DR3, DQ2, DR7, DR1 and DQ5 (10, 11). Mechanisms of molecular mimicry, persistent inflammation due to the absence in purification of immune complexes in which IgA participates, among others, have also been proposed (9).

Regarding the coexistence of SIgAD and JIA, nine studies have described a wide variation in the prevalence of these entities, range from 0 to 15.7% (9). Other rheumatic diseases secondary to SIgAD have also been described, such as rheumatoid arthritis, ankylosing spondylitis, Sjögren's syndrome, systemic sclerosis, lupus, among others (9). In the particular case of idiopathic uveitis and SIgAD, without association to JIA, there are insufficient data to compare prevalence with the general population (12).

Decreases in switched memory B cells ($CD27^+IgM^-IgD^-$), as well as transitional B cells ($CD24^{++}CD38^{++}IgM^{++}$) and plasmablasts ($CD24^-CD38^{++}$) have been documented in patients with SIgAD compared to the general population (13). In this case, the patient has an absence of transitional cells; however, she has switched memory B cells in the normal range for her age (Figure 1) (14). In secondary IgA deficiency an increase in transitional B cells has been reported, contrary to the primary deficit. This could help clarify the difference between primary and secondary IgA deficit (15). Despite this patient has a slight decrease in the naive B cells, no significant differences in this compartment have been demonstrated between

patients with SIgAD and healthy controls (14). B cells $CD21^{low}CD38^{low}$ unique subset have been reported increased in the context of autoimmune diseases as well as SIgAD (13, 16). This description is compatible with the case presented, since the patient has an absolute value of $CD21^{low}CD38^{low}$ of 18 abs/uL cells (5 %) (expected value for age 3-4 abs/uL cells) (14). Many of these immunophenotypic findings can be detected in patients with common variable immunodeficiency (CVID), although the latter entity is usually more pronounced. Based on the possible common genetic background that exists between SIgAD and CVID, this case and similar cases should be strictly observed over time, in order to determine if the patient will develop characteristics more typical for CVID (9).

The immunological evaluation of uveitis includes ANA, HLA-B27 and other autoimmunity markers, but measurement of serum immunoglobulins is usually not considered as part of this evaluation (17). Kubicka studied immunological disturbances in patients with idiopathic posterior uveitis and non-specific abnormalities of immune system parameters were found in 76% (18). Rahimi evaluated immunoglobulins in 51 patients with idiopathic anterior uveitis and no patient had low IgA (19).

A prospective study on arthritis in Costa Rica pointed to the importance of a detailed history of recurrent infections in the study of chronic arthritis. From this study, an immunoglobulin evaluation was scheduled in all children with arthritis before the start of immunosuppressive treatment (7).

CONCLUSION

SIgAD is characterized by a higher incidence of autoimmune diseases, including JIA. Any rheumatological evaluation, should include immunoglobulins, since dysgammaglobulinemia or

hypogammaglobulinemia can develop as a result of the immunosuppressive treatment.

Finally, further clinical studies are needed to determinate the prevalence of primary immunodeficiencies diseases in idiopathic uveitis.

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AUTHOR'S CONTRIBUTION: AAM: conceived and designed the study, collected the data, part of the clinical team in charge of patient care, performed flow cytometric analyzes, wrote the manuscript. GIE: collected the data, part of the clinical team in charge of patient care. JMA: collected the data, part of the clinical team in charge of patient care. MCS: collected the data, part of the clinical team in charge of patient care, performed flow cytometric analyzes. OCJ: performed flow cytometric analyzes, wrote the manuscript. AF: conceived and designed the Study, performed flow cytometric analyzes, wrote the manuscript. All authors reviewed and approved the final version of the manuscript.

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REFERENCIAS

1. Thieffry S, Arthuis M, Aicardi J, Lyon G. [Ataxiatelangiectasis. (7 personal cases)]. *Rev Neurol (Paris)*. 1961; 105: 390-405.
2. Moschese V, Chini L, Graziani S, Sgrulletti M, Gallo V, Di Matteo G, et al. Follow-up and outcome of symptomatic partial or absolute IgA deficiency in children. *Eur J Pediatr*. 2019;178(1):51-60.
3. Yazdani R, Azizi G, Abolhassani H, Aghamohammadi A. Selective IgA Deficiency: Epidemiology, Pathogenesis, Clinical Phenotype, Diagnosis, Prognosis and Management. *Scand J Immunol*. 2017;85(1):3-12.
4. Martini A, Ravelli A, Avcin T, Beresford MW, Burgos-Vargas R, Cuttica R, et al. Toward New Classification Criteria for Juvenile Idiopathic Arthritis: First Steps, *Pediatric Rheumatology International Trials Organization International Consensus*. *J Rheumatol*. 2019;46(2):190-7.
5. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol*. 2004;31(2):390-2.
6. Angeles-Han ST, Ringold S, Beukelman T, Lovell D, Cuello CA, Becker ML, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis-Associated Uveitis. *Arthritis Care Res (Hoboken)*. 2019;71(6):703-16.
7. Arguedas O, Fasth A, Andersson-Gare B, Porras O. Juvenile chronic arthritis in urban San Jose, Costa Rica: a 2 year prospective study. *J Rheumatol*. 1998;25(9):1844-50.
8. Sen ES, Ramanan AV. Juvenile idiopathic arthritis-associated uveitis. *Clin Immunol*. 2020; 211: 108322.
9. Odineal DD, Gershwin ME. The Epidemiology and Clinical Manifestations of Autoimmunity in Selective IgA Deficiency. *Clin Rev Allergy Immunol*. 2020;58(1):107-33.
10. Ferreira RC, Pan-Hammarstrom Q, Graham RR, Fontan G, Lee AT, Ortmann W, et al. High-density SNP mapping of the HLA region identifies multiple independent susceptibility loci associated with selective IgA deficiency. *PLoS Genet*. 2012;8(1):e1002476.
11. Mohammadi J, Ramanujam R, Jarefors S, Rezaei N, Aghamohammadi A, Gregersen PK, et al. IgA deficiency and the MHC: assessment of relative risk and microheterogeneity within the HLA A1 B8, DR3 (8.1) haplotype. *J Clin Immunol*. 2010;30(1):138-43.
12. Dominguez O, Giner MT, Alsina L, Martin MA, Lozano J, Plaza AM. [Clinical phenotypes associated with selective IgA deficiency: a review of 330 cases and a proposed follow-up protocol]. *An Pediatr (Barc)*. 2012;76(5):261-7.
13. Nechvatalova J, Pikulova Z, Stikarovska D, Pesak S, Vlkova M, Litzman J. B-lymphocyte subpopulations in patients with selective IgA deficiency. *J Clin Immunol*. 2012;32(3):441-8.

14. Morbach H, Eichhorn EM, Liese JG, Girschick HJ. Reference values for B cell subpopulations from infancy to adulthood. *Clin Exp Immunol.* 2010;162(2):271-9.
15. Hügler B, Speth F, Warnatz K, Schlesier M, Krumrey-Langkammerer M, Schuster V, et al. Acquisition of Selective IgA Deficiency in Juvenile Idiopathic Arthritis after Immunosuppressive Treatment. *Ann Paediatr Rheumatol.* 2013;2(4):171-7.
16. Thorarinsdottir K, Camponeschi A, Gjertsson I, Martensson IL. CD21⁻/low B cells: A Snapshot of a Unique B Cell Subset in Health and Disease. *Scand J Immunol.* 2015;82(3):254-61.
17. Grumet P, Kodjikian L, de Parisot A, Errera MH, Sedira N, Heron E, et al. Contribution of diagnostic tests for the etiological assessment of uveitis, data from the ULISSE study (Uveitis: Clinical and medicoeconomic evaluation of a standardized strategy of the etiological diagnosis). *Autoimmun Rev.* 2018;17(4):331-43.
18. Kubicka-Trzaska A. [Immunologic disturbances in patients with idiopathic posterior uveitis]. *Klin Oczna.* 2000;102(4):253-8.
19. Rahimi M, Najafi M. The Role of Immune System in Idiopathic Anterior Uveitis. *Iran J Immunol.* 2006;3(2):91-4.