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ORIGINAL ARTICLE

IgA deficiency and autoimmune comorbidities in Juvenile Idiopathic Arthritis☆

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KEYWORDS
Autoimmune diseases;
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Abstract
Objectives: (1) To describe the prevalence of IgA deficiency (IgAD), uveitis, coeliac disease (CD) and thyroid disorders in a multicentric cohort of patients diagnosed with JIA and, (2) to evaluate whether patients with JIA and IgAD present other autoimmune diseases more frequently than patients with normal serum levels of IgA.
Methods: Retrospective chart review of a cohort of patients diagnosed with JIA followed at the paediatric rheumatology units of two hospitals in Madrid, Spain.
Results: A total of 193 patients were included. Of them, 123 were females (64%). Median age at disease onset was 5.6 years (IQR 2.5-9.7) and the median time of follow-up was 5.1 years (IQR 2.2-8.1). The three most common ILAR categories were oligoarticular (53%), polyarticular RF negative (20%) and enthesitis related arthritis (10%). Serum IgA levels were available in 172/193 (89%); 25/172 (15%) had selective (<7mg/dl, n=8) or partial (7-69mg/dl, n=17) IgAD. All the patients had periodic eye exams. Eighteen children (9%) had anterior uveitis, 15/18 chronic and 3/18 acute. Serum anti transglutaminase IgA, or IgG in IgAD were obtained in 135/193

Abbreviations: ANA, Antinuclear antibodies; Anti-TG, Antithyroglobulin antibodies; Anti-TPO, Anti-thyroid peroxidase; ATA, Anti-thyroid antibodies; CD, Coeliac disease; IgAD, IgA deficiency; FTT, Failure to thrive; ILAR, International League of Associations for Rheumatology; IQR, Interquartile range; JIA, Juvenile Idiopathic Arthritis; PID, Primary Immunodeficiency; pIgAD, Partial IgA deficiency; RF, Rheumatoid factor; sIgAD, Selective IgA deficiency; TSH, Thyroid-stimulating hormone.

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(70%). Four children (3%) were diagnosed with CD either by intestinal biopsy (n=3) or by the combination of characteristic clinical, serological and genetic features (n=1); two of them had IgAD (p=0.12; OR=6.4; 95% CI 0.9-47.6). Only 1/153 (0.7%) patient had hyperthyrotropinemia with positive anti-thyroid antibodies and required replacement therapy.
Conclusion: Patients with JIA frequently present autoimmune comorbidities. IgAD does not seem to increase their prevalence, with the possible exception of CD.
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PALABRAS CLAVE
Artritis idiopática juvenil;
Enfermedades autoinmunes;
Deficiencia de IgA;
Enfermedad celiaca;
Enfermedad tiroidea

Deficiencia de IgA y comorbilidades autoinmunes en la artritis idiopática juvenil

Resumen
Objetivos: (1) Describir la prevalencia de deficiencia de IgA (DIgA), uveítis, enfermedad celiaca (EC) y alteraciones tiroideas en una cohorte multicéntrica de pacientes diagnosticados de artritis idiopática juvenil (AIJ) y (2) evaluar si los pacientes con AIJ y DIgA presentan otras enfermedades autoinmunes con más frecuencia que los pacientes con niveles normales de IgA.
Métodos: Estudio retrospectivo de una cohorte de pacientes con AIJ en seguimiento en unidades de Reumatología pediátrica en 2 hospitales de Madrid (España).
Resultados: Se incluyó a 193 pacientes, de los cuales 123 eran mujeres (64%). La edad media al inicio fue 5,6 años (RIC 2,5–9,7) y la mediana de seguimiento 5,1 años (RIC 2,2–8,1). Las 3 categorías ILAR más frecuentes fueron oligoarticular (53%), poliarticular con factor reumatoide negativo (20%) y artritis relacionada con entesitis (10%). Los niveles séricos de IgA estaban disponibles en 172/193 (89%); 25/172 (15%) tenían DIgA, selectiva (<7 mg/dl, n = 8) o parcial (7–69 mg/dl, n = 17). Todos los pacientes tuvieron revisiones oftalmológicas periódicas. Tuvieron uveítis anterior 18 pacientes (9%), 15/18 crónica y 3/18 aguda. Los niveles séricos de antitransglutaminasa IgA (o IgG en pacientes con DIgA) fueron obtenidos en 135/193 (70%); 4 pacientes (3%) fueron diagnosticados de EC por biopsia (n = 3) o por criterios clínicos, serológicos o genéticos (n = 1); 2 de ellos tenían DIgA (p = 0,12; OR = 6,4; IC del 95%, 0,9–47,6). Solo 1/153 (0,7%) tuvo hipertirotropinemia con anticuerpos antitiroideos positivos y requirió tratamiento.
Conclusión: Los pacientes con AIJ presentan comorbilidades autoinmunes con frecuencia. La DIgA no parece aumentar su prevalencia, con la posible excepción de la EC.
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Introduction

IgA deficiency (IgAD) is the most common primary immunodeficiency (PID),[1,2] with a prevalence of 1:200 to 1:600 Caucasians. In addition, it is the PID that most frequently associates autoimmune phenomena; between 25-32% of individuals with IgAD are diagnosed with an autoimmune disease.[1]

Juvenile idiopathic arthritis (JIA) is the most frequent chronic rheumatic disease of childhood, with a prevalence of 1–2 cases per 2000 children under 16 years of age.[3–5] JIA is not a single disease but rather an umbrella term that includes 7 different forms of juvenile arthritis with different pathogenesis, genetics and clinical manifestations.[6,7] Patients with JIA present IgAD[1,8–12] and other autoimmune diseases, such as uveitis,[13,14] coeliac disease[15–17] (CD) or thyroid disorders[18–21] at higher frequency than in the general population.

The objectives of the study were (1) to describe the prevalence of IgAD, uveitis, CD and thyroid disorders in a multicentric cohort of patients diagnosed with JIA and, (2) to evaluate whether patients with JIA and IgAD present other autoimmune diseases more frequently than patients with JIA and normal serum levels of IgA.

Patients and methods

The study is a retrospective chart review of a cohort of patients with JIA followed at the paediatric rheumatology units of two hospitals in the Madrid region, Spain from March 2008 to March 2020.

JIA patients were classified according to the International League of Associations for Rheumatology (ILAR) criteria.[3] *Systemic arthritis* was defined as arthritis with or preceded by fever of at least 2 weeks' duration and one of the following, evanescent rash, lymph node enlargement, hepato or splenomegaly, or serositis; *Oligoarthritis* as arthritis affecting one to 4 joints during the first 6 months of disease; *Polyarthritis*,definedas arthritis in 5 or more joints during the first 6 months of disease, may be further classified into rheumatoid factor *(RF) positive*, if 2 or more tests for RF at least 3 months apart were positive during the first 6

months of disease, or *RF negative*. Other categories included *Enthesitis related arthritis*, characterized by involvement of the entheses and/or axial skeleton, and*Psoriatic Arthritis*. Finally, a diagnosis of *Undifferentiated arthritis* was made when arthritis fulfilled criteria in no category or in two or more of the above.

Immunoglobulin levels (IgG, IgM, and IgA) were usually measured at diagnosis. Children with low levels of IgA underwent retesting after 6–12 months and, if they were aged less than 4 years, after they turned 4. If their concentration was normal no further determination was required. IgA deficiency (IgAD) was considered when serum IgA levels were <70 mg/dl with normal levels of IgM and IgG in children older than four years of life.[2] IgAD was further classified as selective IgAD (sIgAD) if the IgA level was less than 7 mg/dL and partial IgAD (pIgAD) if the level was between 7 and 69 mg/dL.

Uveitis was defined according to SUN (Standardization of Uveitis Nomenclature),[22] considering anterior uveitis as clinically evidenced inflammation of the anterior chamber of the eye. The terms *acute* and *chronic* described its clinical course. Uveitis screening followed the intervals recommended by the American Academy of Paediatrics.[23] Accordingly, ophthalmologic examinations were performed every 3-12 months, depending on individual risk assessment.

Coeliac disease was defined according to the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) criteria[24] In non-IgA deficient patients, antibody titres at least 10 times the upper limit of normal of IgA anti-transglutaminase and positive anti-endomysial antibodies was considered diagnostic. In the presence of IgA deficiency or in patients with diagnostic doubts other criteria may be used, including elevation of IgG antibodies, HLA DQ2/DQ8 determination or compatible findings at duodenal histology. Considering the retrospective nature of the cohort, most of the patients had confirmation by intestinal biopsy. CD serology was usually obtained at presentation. Patients with high levels of anti-transglutaminase antibodies were referred to Gastroenterology, whereas those with normal levels did not require further determination.If new symptoms appeared during the follow-up repeated serology was evaluated on a patient-by-patient basis.

Antinuclear antibodies (ANA) and RF were defined as 2 positive results separated 12 weeks during the first 6 months of illness.[25] ANA screening was performed using a multiparametric Multiplex autoantibody assay. ANA positivity was confirmed by indirect immunofluorescence, considering positive a cut-off titre of 1/80.

Thyroid-stimulating hormone (TSH) concentration was considered normal up to 5 mIU/l, whereas T4 was considered decreased when its serum level was <0.8 ng/dl. The screening protocol at our centres was based on obtaining an annual TSH level and, if elevated, ordered anti-thyroid antibodies.

Data were obtained from clinical records and anonymized for database collection. Statistical analysis was performed using SPSS® Statistics v24. Descriptive measurements were expressed as median and interquartile range (IQR) and chi-square test was used for hypothesis testing between qualitative variables. The study received the approval of the local ethics committee (CEIm number 20/439).

Results

Demographic characteristics of the cohort

A total of 193 JIA patients were included in the study. There were 123 females (64%). The median age at disease onset was 5.6 years (IQR 2.5-9.7) and the median follow-up time was 5.1 years (IQR 2.2-8.1).

The most common JIA category was Oligoarticular (53%), followed by Polyarticular RF negative (20%) and Enthesitis related arthritis (10%) (Table 1). Median time between onset of symptoms and first consultation with a paediatric rheumatologist was 2.3 months (IQR 0.9-6.3).

IgA deficiency

Serum IgA level was available for review in 172 patients (89%). Median value of IgA was 127 mg/dl (IQR 80-202). Out of 172 patients, 34 (20%) had selective (n=8, 5%) or partial IgA deficiency (n=26, 15%), with a female preponderance (27/34, 79%).

Regarding patients with sIgAD, 3 out of 8 associated other comorbidities. One was a female diagnosed with ANA negative oligoarthritis and chronic anterior uveitis. The second was another female with ANA positive oligoarticular JIA and coeliac disease. The last patient was also a female diagnosed with Turner's syndrome, oligoarthritis and persistent hyper-

Table 1 Demographic and clinical characteristics of the study sample based on the ILAR classification.

JIA category	Patients, *n* (%)	Female, *n* (%)	Age at onset in years. Median (IQR)	ANA-positive, *n* (%)	RF-positive, *n* (%)	HLA-B27-positive, *n* (%)
Systemic onset	13 (7%)	4 (31%)	4.5 (1.9—9.6)	0	0	0
Oligoarthritis	103 (53%)	74 (72%)	4.0 (2.4—7.7)	11 (11%)	1 (1%)	9 (9%)
RF – polyarthritis	39 (20%)	28 (72%)	7.7 (2.5—10.7)	2 (5%)	0	3 (8%)
RF + polyarthritis	2 (1%)	2 (100%)	11.3 (8.1—14.5)	0	2 (100%)	0
ErA	20 (10%)	5 (25%)	8.5 (6.5—10.9)	0	0	13 (65%)
Psoriatic arthritis	6 (3%)	4 (67%)	3.4 (1.9—8)	0	0	2 (33%)
Undifferentiated arthritis	10 (5%)	6 (60%)	2.7 (0.8—9.5)	2 (20%)	0	4 (40%)

ANA, antinuclear antibodies; ErA, enthesitis-related arthritis; HLA, human leukocyte antigen; IQR, Interquartile range; JIA, juvenile idiopathic arthritis; RF, Rheumatoid factor.

Table 2 IgA deficiency and other autoimmune conditions present in the study sample, ILAR classification.

JIA category	IgAD (%)	Uveitis (%)	Coeliac disease (%)	Hyperthyrotropinaemia (%)
Total	25/172 (15%)	18/193 (9%)	4/135 (3%)	14/153 (9%)
Systemic onset	0/11	0/13	0/8	2/10 (20%)
Oligoarthritis	17/89 (19%)	11/103 (11%)	3/72 (4%)	9/79 (11%)
RF − polyarthritis	5/37 (14%)	2/39 (5%)	1/28 (4%)	2/34 (6%)
RF + polyarthritis	0/2	0/2	0/1	0/2
ErA	0/19	0/20	0/14	0/14
Psoriatic arthritis	0/5	2/6 (33)	0/4	0/6
Undifferentiated arthritis	3/9 (33%)	3/10 (30%)	0/8	1/8 (13%)

ErA, enthesitis-related arthritis; IgAD, IgA deficiency; RF, rheumatoid factor.

thyrotropinemia (TSH 8 ng/ml) but normal T4 value who did not require replacement therapy.

A second determination of IgA levels was performed in 25 out of 34 patients (74%) with sIgAD (8/8) or pIgAD (17/26) after a median of 31 months (IQR 11-57). IgA levels were >70 mg/dl in this determination in 9 patients, all with pIgAD. Therefore, at the end of the follow-up, a significant proportion of children with pIgAD normalize their IgA levels whereas the 8 children with persistent sIgAD maintained almost undetectable IgA levels. (Table 2).

Out of 25 patients with IgAD, 17 had oligoarthritis (17/89, 19%) and 5 polyarthritis RF negative (5/37, 14%).

All the patients with sIgAD were followed at the immunodeficiency unit of one of the participating hospitals, and none of them progressed to a more severe form of disease, such as Common Variable Immunodeficiency.

The relationship between IgAD and other autoimmune conditions was studied. No statistically significant association was found between IgAD and uveitis, coeliac disease or hyperthyrotropinemia.

None of the patients with IgAD had major infectious complications attributable to IgA deficiency.

Uveitis

Periodic ophthalmologic assessment was performed in all patients (Table 2). Median time between first paediatric rheumatology consultation and first ophthalmologic assessment was 1.4 months (IQR 0.5-3.1). Eighteen patients (9%) were diagnosed with anterior uveitis, 15/18 (83%) with chronic and 3/18 (17%) with acute anterior uveitis. Fifteen were females (83%, OR= 3.2; 95% CI 0.9-11.3). The median age at uveitis diagnosis was 6.1 years old (IQR 3.8-8.5), whereas median time between JIA onset and uveitis diagnosis was 23.9 months (3.5-52). Four patients (22%) developed uveitis prior to or simultaneously with joint disease.

Anterior uveitis was present in children with oligoarthritis (11%), polyarthritis RF negative (5%), psoriatic arthritis (33%) and undifferentiated arthritis (30%) (Table 2). The three patients with undifferentiated arthritis and acute anterior uveitis met ILAR criteria for ErA but had family history of psoriasis in a first-degree relative.[3]

As expected, uveitis was more common in ANA-positive patients (OR= 4.2; 95% CI 1.2-15) and patients younger than 6 years (OR= 2.5; 95% CI 0.9-7.4).

Out of 18 patients with anterior uveitis 3 had IgAD (17%), 1 selective and 2 partial; no statistically significant association was found with IgAD.

Coeliac disease

Serum anti-transglutaminase IgA levels, or IgG in IgAD, were available in 135 patients (70%). CD was diagnosed in 4 (3%) patients, 3 with oligoarthritis and 1 with polyarthritis RF negative. Two of the patients were women. Biopsy was obtained in 3 patients confirming the disease. The fourth had typical clinical, serological and genetic features. Three patients were diagnosed with CD before JIA diagnosis. One girl had failure to thrive (FTT) and chronic diarrhoea 5 years before the joint disease started, the other two had FTT few months before developing arthritis. The fourth patient had neither gastrointestinal complaints nor FTT. He was diagnosed with JIA, presenting very high titres of anti-transglutaminase IgA in the initial screen. Diagnosis was confirmed by duodenal biopsy.

Two out of 4 children with CD had IgAD (p=0.12; OR=6.4; 95% CI 0.9-47.6), selective in one patient and partial in the other, confirmed on several occasions. A third patient had an IgA level towards the lower limit of normal, 71 mg/dl.

Thyroid disease

Thyroid-stimulating hormone (TSH) measurement was available in 153 patients (79%). Hyperthyrotropinemia was found in 14 (9%) children, 10/14 were females (71%). Only 1 patient (0.6%), a girl with ANA negative oligoarticular disease and normal IgA serum levels, was positive for anti-thyroglobulin and anti-thyroid peroxidase antibodies, and required pharmacological replacement therapy. All the other children had transient hyperthyrotropinemia.

Discussion

This study revealed that patients with JIA and IgAD did not present autoimmune conditions more frequently than patients with juvenile arthritis and normal serum IgA levels. The elevated proportion of children with JIA and coeliac disease who had IgAD will be discussed below.

This result was somewhat unexpected because IgA deficiency is the primary immunodeficiency more frequently associated with autoimmune conditions, including JIA,

coeliac disease, type 1 diabetes, thyroid disorders and systemic lupus erythematosus.[2] On the other hand, autoimmune comorbidities are also more common in JIA, affecting 2.2%–15.2% of patients.[18,26]

Our cohort confirmed that IgAD was a common finding in patients with JIA. In our series 15% of the children had serum IgA levels of less than 70 mg/dl, including 5% who meet the criteria for sIgAD. This prevalence is higher than that reported by Moradinejad et al in Iran[8] (8.3% of 83 patients, 1.2% with sIgAD and 7.1% with pIgAD), Spârchez et al. in Romania[9] (2.4% of 84 patients, all sIgAD), and Panush et al[10] (1.7% of patients with sIgAD out of a total of 176) and Bluestone et al[11] (1% with sIgAD out of 200 consecutive Juvenile Rheumatoid Arthritis) in the United States. . On the other hand, two series with more than 100 juvenile arthritis patients each, one from Scandinavia and the other from the US, recorded a prevalence of sIgAD of 4.3%,[12] very similar to that obtained in our study.

[1,27]The explanation for these differences is that the prevalence of IgAD varies worldwide depending on the ethnic background, being most prevalent in Caucasians. It ranges from 1:163 in Spain, to 1:651 in Iran, 1:875 in England or 1:18,550 in Japan. In the United States, the prevalence of IgAD ranges from 1:223 to 1:1000 in community-based studies.[28] Most authors, however, have reported the prevalence of sIgAD but not of pIgAD. A recent study addressed the question of whether only sIgAD was associated with autoimmune disorders. Moschese et al[29] studied 80 patients with IgAD (selective in 44 and partial in 36) with a mean duration of follow-up of 5 years. At the end of the follow-up, 18% of the patients with pIgAD and 8% of those with sIgAD had autoimmune disorders such as CD, thyroiditis or diabetes. Interestingly, autoimmunity was not identified in any patients with normal IgA levels. Other authors have also reported a greater frequency of autoimmunity in children and adults with pIgAD.[30,31]

In addition, Moschese et al[29] observed that 33% of patients with pIgAD versus 9% of those with sIgAD evolved to IgA concentration normalization. In our study, we registered a higher IgA normalization rate among patients with pIgAD (53%) and lower among sIgAD (none). None of the patients developed a more severe form of antibody deficiency as it has been reported elsewhere.[32]

Uveitis is the most frequent extra-articular manifestation of JIA. It may cause severe vision impairment and decrease quality of life.[33] JIA-associated uveitis is characteristically present in children with early-onset ANA-positive arthritis,[13,14] as observed in our series. The prevalence of uveitis in the cohort (9%) was similar to that reported in other series (12%–13%).[13,14] The distribution of uveitis was similar in patients with and without IgAD, suggesting that IgA levels are not relevant for this condition.

In regards to CD, the disease has been widely associated with sIgAD. Around 0.6-2% of coeliac patients have sIgAD,[2] while the prevalence of CD in patients with sIgAD patients is approximately 6%, compared to an estimated 1% in the general population.[1]

The prevalence of CD in our cohort was 3%, similar to the prevalence found by other authors. Nisihara et al. reported that 8.8% of a total of 45 patients with JIA had positive IgA or IgG anti-transglutaminase antibodies; however, none of their patients had gastrointestinal symptoms and none of their families authorized an endoscopy.[34] Alpigiani et al. found that 3 out of 108 children with JIA (2.8%) had positive CD-specific antibodies and biopsy-confirmed disease, none of whom had sIgAD.[15] Öman et al. screened 213 patients with JIA in Sweden for anti-transglutaminase antibodies and performed an intestinal biopsy when indicated,[16] and found a prevalence of CD associated with JIA of 2.8% (95% CI, 0.6%–5%). Skrabl-Baumgartner et al. also used an anti-transglutaminase antibodies-based screening strategy, performing HLA typing and small intestinal biopsy in their 95 patients with JIA. Four out of 95 (4.2%) were diagnosed with CD.[17] None of the patients had sIgAD.

Interestingly, half the children with JIA and CD in our cohort had IgAD (1 with sIgAD and 1 with pIgAD). Although the proportion did not reach levels of statistical significance its OR suggested that it was probably due to low statistical power arising from the small sample size. Most authors do not report the number of patients with CD and pIgAD, not being possible to ascertain to what extent serum IgA levels of less than 70 mg/dl were present in their patients. As was discussed above, IgA deficiency is associated with autoimmune phenomena regardless of its serum level.

Thyroid disorders have also been described in patients with JIA, particularly hyperthyrotropinaemia and subclinical hypothyroidism. In our cohort, the prevalence of hyperthyrotropinaemia was 9%. Most patients, however, had transient elevation of TSH and did not receive any treatment. In fact, only 1 patient (0.7%) was positive for anti-thyroid antibodies (ATA) and required chronic replacement therapy. Therefore, it is important to differentiate between patients with autoimmune thyroiditis and children with isolated hyperthyrotropinaemia, which is usually transient. Harel et al. studied 66 children with JIA and detected elevated TSH levels in 8/66 (12%), with positive antithyroglobulin (anti-TG) and anti-thyroid peroxidase (anti-TPO) in 7/62 (11.3%) and 5/65 (7.9%) respectively..[19] All patients with ATA had oligoarticular disease. Alpigiani et al. found a similar prevalence of ATA (9/66 patients; 14%).[20] All were female, and 8 had oligoarticular disease. Three tested positive for anti-TG, 5 for anti-TPO and 1 for both. On the other hand, all children had normal concentrations of TSH, free triiodothyronine (T3) and free T4.

Tronconi et al[18] found a similar prevalence of positive ATA in a series of 79 children with JIA (8/79; 10.1%). Eight tested positive for anti-TG, associated with anti-TPO in 5. Six of them had oligoarticular disease. Two other patients had elevated TSH with negative ATA. Other authors have reported a lower prevalence. Unsal et al. found that out of 80 patients with JIA, 4 (5%) had ATA, 2 with elevated levels of TSH and a third one with hyperthyroidism.[35] Finally, Alvarez Madrid et al reported that 3 children of their series of 115 Spanish patients with JIA (2.6%) had ATA with abnormal levels of TSH.[21]

We do not have an explanation for the low prevalence of hyperthyrotropinaemia and thyroid disorders found in our cohort. The screening protocol in our hospitals is based on the measurement of TSH levels once a year and, if elevated, testing for anti-thyroid antibodies.

None of the patients with systemic JIA received a diagnosis of autoimmune disorder, and only 2 had transient hyperthyrotropinaemia. This is consistent with the non-autoimmune pathogenesis of this form of JIA.

There are limitations to our study. Given the retrospective nature of the cohort a number of patients lacked data on serum IgA levels, TSH concentration or anti-transglutaminase antibodies. For the first two conditions missing data affected 10% and 20% of the patients respectively, but for CD this number was as high as 30%. On the other hand, a large number of patients were studied, representing one of the largest series that had studied the frequency of hyperthyrotropinemia and CD in patients with JIA to date. In regards to CD, most children with the disease were symptomatic and the prevalence of the disease obtained in our series was similar to that previously reported.

The strengths of the study include the relatively large sample size and its multicentre design. Considering that IgAD is more common in Spaniards compared to other populations, we expected a higher number of patients with IgAD, as was indeed the case, which increased the statistical power of the analysis.

Conclusion

The contribution of IgAD to the burden of autoimmune disease recorded in patients with JIA was explored in a large multicentric cohort. Patients with JIA and IgAD presented uveitis, coeliac disease and hyperthyrotropinemia with the same frequency than patients with normal serum IgA levels.

Conflict of interest

The authors declare that they have no conflict of interest.

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