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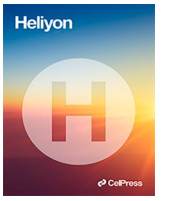

Serum immunoglobulin A (IgA) levels in children affected with Juvenile Idiopathic Arthritis

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ABSTRACT

Background and objective: Immunoglobulin A (IgA) is the most abundant antibody isotype in the human body, considering its presence on the mucosal surfaces, in addition to the amount circulating in the bloodstream. Serum IgA levels can be variably altered in several pathological settings. However, very few studies specifically investigated serum IgA in Juvenile Idiopathic Arthritis (JIA). In the present study, we specifically assessed serum IgA levels in our cohort of patients affected with JIA.

Methods: In this cross-sectional study, serum IgA levels were measured in patients with JIA (and age-matched controls) and analyzed according to age class. The correlation of serum IgA levels with hematological, inflammatory, and disease activity parameters was assessed.

Results: No significant difference in the frequency of low IgA levels (according to the definition of complete and partial IgA deficiency) was observed between JIA patients and controls, overall. This pediatric study population showed a progressive increase of total serum IgA concentrations with age, as expected; however, in JIA patients aged 10–17 years, total IgA serum levels resulted to be significantly higher than in age-matched control subjects. No clear correlation between IgA levels and the examined inflammatory, hematological, and disease activity parameters was observed in JIA patients, except for the erythrocyte sedimentation rate (ESR) in oligoarticular JIA patients: here, serum IgA levels showed a positive and moderate covariation with ESR, which was also observed for disease activity (JADAS-10) in selected oJIA patients without biological therapy.

Conclusions: In our cohort of JIA patients, total serum IgA levels were not reduced and were actually increased in adolescents compared to controls. Larger studies are needed to confirm this

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finding, which cannot be certainly explained based on the available data in this study, even though JIA disease control and/or chronic inflammation may be implicated to some extent.

1. Introduction

Immunoglobulin A (IgA) accounts for >70% of the total antibody pool in the human body and, thus, represents the most abundant antibody isotype overall, although Immunoglobulin G (IgG) serum concentration is much greater than that of circulating IgA. Indeed, IgA is also secreted as dimeric forms across the mucosal surfaces of respiratory, intestinal, and genitourinary system, where it plays a role to protect the host from infections and, in general, also contribute to the homeostasis of microbiota; in this regard, IgA has been proposed to have an immunomodulatory function towards these microorganisms and, probably, dietary antigens as well, since it may (down-)regulate the expression of pro-inflammatory factors and, thus, maintaining the appropriate immunological balance at the mucosal level [1–4].

IgA Deficiency (IgAD) is the most common primary immunodeficiency with an indicative prevalence in the general population of around 1:400. According to the European Society for Immunodeficiencies, complete IgAD is defined by total serum IgA levels <7 mg/dl, whereas total serum IgA levels comprised between 7 mg/dl and the lower limit of the normal range indicate partial or incomplete IgAD [4–6]. Notably, IgAD has been implicated in the development of autoimmunity, in general [7–9]. Indeed, according to different studies, at least 5–30% of IgAD patients are diagnosed with concomitant autoimmune disorders, including idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, autoimmune thyroiditis, type 1 diabetes mellitus, autoimmune hepatitis, celiac diseases, and others [9–11]. Moreover, IgAD has been linked to some specific HLA haplotypes, which may predispose to specific autoimmune diseases [8].

Although several studies suggested an association between IgAD and rheumatoid arthritis in adults, few studies specifically investigated IgA levels in children affected with Juvenile Idiopathic Arthritis (JIA) [7]. JIA is defined as a primary chronic arthritis until 16 years of age. According to the International League of Associations for Rheumatology (ILAR), five main subtypes can be defined inside the JIA classification: systemic (sJIA); oligoarticular (oJIA), which may be persistent or extended; polyarticular (pJIA), which is usually rheumatoid factor (RF) negative and, much less frequently, positive; psoriatic (PsJIA); and enthesitis-related (ERA). Additionally, JIA may be categorized as undifferentiated, if arthritis does not fulfill the diagnostic criteria for any of the aforementioned subtypes [12]. The therapeutic approach is variable according to JIA subtypes, disease activity and comorbidities (e.g. uveitis, inflammatory bowel disorders, others): overall, conventional disease-modifying antirheumatic drugs (cDMARDs), such as methotrexate, and biologic disease-modifying antirheumatic drugs (bDMARDs), especially etanercept and adalimumab, can be used as a maintenance therapy; non-steroidal anti-inflammatory drugs (NSAIDs) and systemic/intra-articular steroids are mainly used for inducing remission at the onset of disease or in case of flares [13–15].

In the present study, we specifically assessed serum IgA levels in our cohort of JIA patients and analyzed them with respect to routine hematological, inflammatory, and disease activity parameters.

2. Materials and methods

2.1. Study design and population

In this cross-sectional study, the main objective was to assess serum IgA levels in patients with JIA during the study period (June 1st, 2020–May 31st, 2022).

The study group included all consecutive pediatric patients (1–17 years old) affected with JIA (diagnosed according to the International League of Associations for Rheumatology – ILAR – criteria) [12], whose guardians accepted to give their consent for their children to participate in this study. The control group included pediatric patients (1–17 years old) visited at the outpatient department for chronic gastrointestinal complaints without any final diagnosis of organic disease (after the appropriate diagnostic work-up) and for whom guardians accepted to give their consent for their children to participate in this study.

This study was carried out at Clinical Academic Department of Pediatrics at University Medical Center (UMC), affiliated with the Nazarbayev University School of Medicine (NUSOM), in Astana (Kazakhstan). The study was approved by both the Institutional Research Ethical Committee of the Nazarbayev University (application n. 205/28112019, approved on January 23rd, 2020) and the Institutional Review Board of UMC (decision n.2.1, approved on December 19th, 2019). Patients' guardians signed the informed consent allowing their children to participate in this research. This research has been performed in accordance with the Declaration of Helsinki.

2.2. Measurement of total serum IgA levels

After collection, all the serum samples were stored at −80 °C and were analyzed in six batches. The quantitative measurement of the total immunoglobulin A (IgA) in serum samples was done by using an immunoturbidimetric assay: in detail, Beckman Coulter AU 680 analyzer and OSR61171 Kit were used. The age-related reference values provided by the laboratory for total serum IgA were as follows: 20–100 mg/dl (1–3 years); 27–195 mg/dl (4–6 years); 34–305 mg/dl (7–9 years); 53–204 mg/dl (10–11 years); 0.58–3.58 mg/dl (12–13 years); 47–249 mg/dl (14–15 years); 61–348 mg/dl (16–17 years).

2.3. Data collection

Secondary (existing) demographic (age, gender) and clinical (main diagnosis and, in detail, JIA subtype for the study groups) were collected for all study participants. Moreover, laboratory data (complete blood cell count: hemoglobin - Hb -, platelets – Plt. -, white blood cells - WBC -, leukocytes subtypes, including lymphocytes – Lymph. – and neutrophils – Neutr. -, expressed as percentages; inflammatory parameters: c-reactive protein - CRP -, erythrocyte sedimentation rate - ESR -) were also available for most of the JIA patients, in addition to information on the ongoing conventional and biological therapy at the moment of the serum samples collection (systemic or intra-articular steroid therapy was not present as a maintenance therapy at the hospital admission). Disease activity was estimated by Juvenile Arthritis Disease Activity Score 10 (JADAS-10) [16]. Data collection was carried out by Microsoft® Excel 2022 for Mac (version 16.68).

2.4. Statistical analysis

Differences in categorical variables were analyzed through Chi-square test; p-value <0.05 was considered statistically significant. Continuous variables were expressed as mean (M)±standard deviation (SD). Differences between two groups were analyzed by two-tailed unpaired *t*-test (with Welch's correction). A p-value <0.05 was considered as statistically significant.

The covariation matrix was computed through Pearson correlation coefficients, in order to assess how two variables can vary together ($r = 0$: two variables do not vary together at all; $0 > r > 1$: two variables tend to increase or decrease together; $r = 1.0$: perfect correlation; $-1 > r > 0$: one variable increases as the other decreases; $r = -1.0$: perfect inverse correlation). A correlation is considered weak, moderate, and strong based on the r absolute value (respectively, <0.4, 0.4–0.7, and >0.7) [17,18]. Descriptive and statistical analyses were made by Prism 9 for MacOS (version 9.3.1, GraphPad Software).

3. Results

3.1. Demographics and clinical characteristics of the study population

During the study period, 488 pediatric patients underwent measurement of serum IgA levels. Considering that serum IgA levels are age-dependent in the pediatric population, both study and control groups have been divided into different age classes (1–3 years; 4–6 years; 7–9 years; 10–13 years; and 14–17 years), according to the laboratory reference values for serum IgA measurement. The number, demographic characteristics, and main diagnosis of the study groups ($n = 289$) and controls ($n = 199$) are summarized in Table 1. Table 2 provides detailed information regarding the JIA subtypes of patients included in the study group; control patients were finally labeled as affected by gastrointestinal functional disorders, thus without any evidence of organic and, in detail, inflammatory and/or autoimmune diseases. Inside each age class, there was no statistically significant difference in terms of age and gender ratio between JIA and control groups.

Table 1
Main demographic characteristics of the study population.

Study Participants	Study Group	Control Group	Study Population
Definition	Juvenile Idiopathic Arthritis	Gastrointestinal Functional Disorders	Total
Patients [N]	289	199	488
1–3 years [N]	28	39	67
Age [M±SD years]	2.8 ± 0.7	3.1 ± 0.7	3.0 ± 0.7
M:F [N]	10:18	18:21	28:39
4–6 years [N]	48	62	110
Age [M±SD years]	5.4 ± 0.8	5.3 ± 0.9	5.4 ± 0.8
M:F [N]	18:30	28:34	46:64
7–9 years [N]	61	32	93
Age [M±SD years]	8.5 ± 0.8	8.4 ± 0.9	8.5 ± 0.8
M:F [N]	25:36	18:14	43:50
10–13 years [N]	77	36	113
Age [M±SD years]	12.1 ± 1.1	11.6 ± 1.1	11.9 ± 1.1
M:F [N]	36:41	17:19	53:60
14–17 years [N]	75	30	105
Age [M±SD years]	15.5 ± 1.0	15.6 ± 1.2	15.5 ± 1.0
M:F [N]	36:39	9:21	45:60

Table 2
Composition of JIA population in terms of JIA subtypes.

Patients	Age Classes					
	1–3 yrs	4–6 yrs	7–9 yrs	10–13 yrs	14–17 yrs	Total
Juvenile Idiopathic Arthritis	**28**	**48**	**61**	**77**	**75**	**289**
- oligo-articular (oJIA)	20 *(71.4%)*	36 *(75.0%)*	38 *(62.3%)*	46 *(59.7%)*	30 *(40.0%)*	170 *(58.8%)*
- poly-articular (pJIA)	2 *(7.1%)*	4 *(14.3%)*	12 *(19.7%)*	16 *(20.8%)*	21 *(28.0%)*	55 *(19.0%)*
- systemic (sJIA)	5 *(17.9%)*	5 *(10.4%)*	8 *(13.1%)*	3 *(3.9%)*	5 *(6.7%)*	26 *(9.0%)*
- enthesitis-related (ERA)	-(0%)	*-(0%)*	2 *(3.3%)*	7 *(9.1%)*	13 *(17.3%)*	22 *(7.6%)*
- psoriatic (PsJIA)	*-(0%)*	1 *(2.1%)*	1 *(1.6%)*	4 *(5.2%)*	2 *(2.7%)*	8 *(2.8%)*
- undifferentiated (iJIA)	1 *(3.6%)*	2 *(4.2%)*	*-(0%)*	1 *(1.3%)*	4 *(5.3%)*	8 *(2.8%)*

3.2. Frequency of low-IgA patients

In the whole study population, 10 patients with total serum IgA levels <7 mg/dl (consistent with complete IgA deficiency) were identified, accounting for a 2.05% of the study population, overall. Both the JIA and control groups included 5 children with IgA levels <7 mg/dl, corresponding to a frequency of 1.73% and 2.51%, respectively; however, this difference was not statistically significant. Unfortunately, due to the financial resource limitations, we could not concomitantly measure serum IgG and IgM levels, which does not allow us to distinguish patients with selective IgA deficiency from patients with IgA deficiency as part of another primary immunodeficiency.

Notably, according to the laboratory reference values, 5 additional patients showed total serum IgA levels ≥7 mg/dl, but under the lower limit of the normal age-related ranges. All these children were part of the control group.

3.3. Analysis of total serum IgA levels in JIA patients according to patients' age classes

We compared total serum IgA levels between JIA and control patients, after excluding those children having low IgA levels potentially consistent with partial of complete IgAD. As showed in Fig. 1A, the study population showed a progressive increase of total serum IgA concentrations with increasing age class (1–3 years: 73.8 ± 40.7 mg/dl; 4–6 years: 114.1 ± 72.0 mg/dl; 7–9 years: 156.3 ± 79.0 mg/dl; 10–13 years: 186.2 ± 98.0 mg/dl; 14–17 years: 196.8 ± 88.7 mg/dl), as expected. This trend is present in both JIA and control groups individually. Nonetheless, the total IgA serum levels resulted to increase to a lesser rate in the control group compared to the JIA patients during the adolescent age, so that a significant differences between these groups was observed in the 10–13 years old (JIA: 201.5 ± 108.3 mg/dl; controls: 150.0 ± 53.5 mg/dl; $p = 0.0014$) and 14–17 years old patients (JIA: 209.7 ± 95.5 mg/dl; controls: 163.4 ± 57.2 mg/dl; $p = 0.0033$), as highlighted in Fig. 1B; whereas the IgA values were similar between younger JIA (1–3 years: 74.9 ± 37.5 mg/dl; 4–6 years: 113.9 ± 90.1 mg/dl; 7–9 years: 160.7 ± 87.7 mg/dl) and control (1–3 years: 72.9 ± 43.2 mg/dl; 4–6 years: 114.3 ± 54-6 mg/dl; 7–9 years: 147.9 ± 58.8 mg/dl) groups.

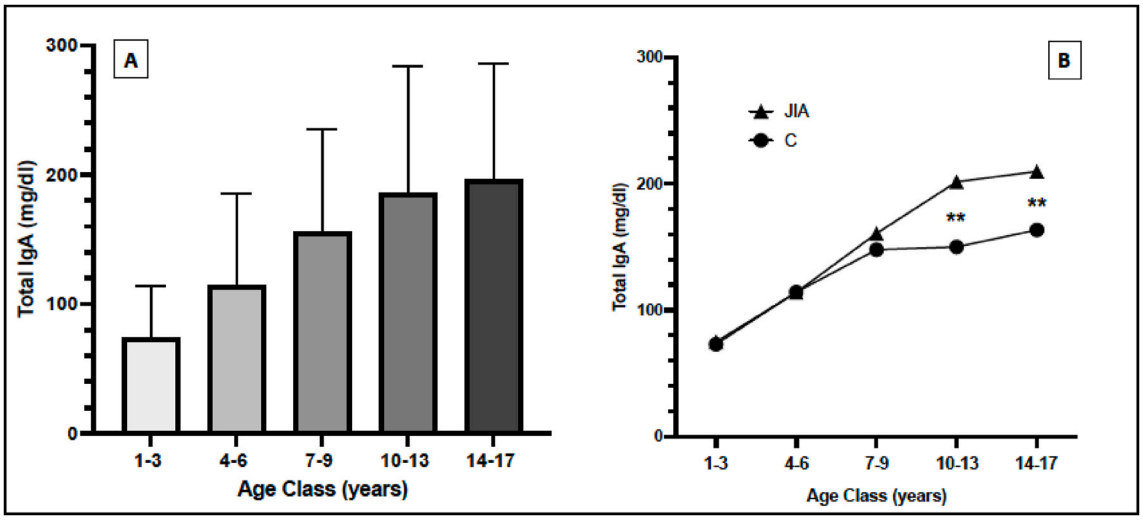

Fig. 1. Total serum IgA according to the age class in the study population (panel A; bars correspond to SD) and age-related trend in the JIA and control study groups (panel B; [**: $p < 0.01$].

3.4. Correlation analysis of total serum IgA levels

Secondary data on the main inflammatory indexes (ESR and CRP), disease activity (JADAS-10) and hematological parameters (WBC, Hb, Plt., Neutr., Lymph.) were available for most patients only for the JIA groups (unfortunately, the number of controls with all these analyses available exactly at the time of the serum sample collection, was insufficient for the statistical analysis).

As shown in Table 3, there was no correlation between serum IgA levels and JADAS-10 score as well as all the examined inflammatory and hematological parameters in JIA patients, except only in the 1–3 years age group as regards ESR, which showed a strong level of positive covariation ($r = 0.760$; $p < 0.001$). Notably, this is the youngest age group of JIA children, wherein the great majority of patients (25 out of 28; 89.2%) is represented by oligoarticular forms (oJIA).

Therefore, we decided to specifically analyze the covariation in oJIA patients: interestingly, a positive and at least moderate correlation between total IgA levels and ESR was then observed in all the age groups (1–3 years: $r = 0.762$, $p < 0.001$; 4–6 years: $r = 0.557$, $p = 0.001$; 7–9 years: $r = 0.523$, $p = 0.003$; 10–13 years: $r = 0.634$, $p < 0.001$; 14–17 years: $r = 0.595$, $p = 0.001$). However, no significant correlation was present between IgA levels and JADAS-10 score in oJIA children, except for the group aged 10–13 years ($r = 0.636$; $p < 0.001$).

Notably, as highlighted in Table 4, the maintenance therapy in oJIA patients significantly differed from other subtypes of JIA patients in terms of use of both bDMARDs ($p = 0.0001$) and cDMARDs other than methotrexate ($p = 0.0061$), which was definitely greater in the latter categories of patients. Therefore, we tried to assess oJIA patients without bDMARDs maintenance therapy, in order to analyze the covariation among serum IgA levels, ESR and JADAS-10 in a sufficiently numerous, clinically homogeneous subgroup, and free from biologics (which directly inhibits the pro-inflammatory cytokines). In Fig. 2, we summarized this analysis including these patients for whom all these three parameters (serum IgA levels, ESR and JADAS-10) were all known. In this oJIA subgroup receiving methotrexate as maintenance therapy and/or only intra-articular steroids as needed, the positive covariation between serum IgA levels was more evident than that computed for all oJIA patients, regardless of the maintenance therapy (which was previously shown in Table 3). Notably, in these relatively homogeneous oJIA patients free from DMARDs, also JADAS-10 showed a much better covariation with serum IgA levels, since all age groups showed a positive and moderate correlation (1–3 years: $r = 0.595$, $p = 0.071$; 4–6 years: $r = 0.465$, $p = 0.045$; 7–9 years: $r = 0.402$, $p = 0.088$; 10–13 years: $r = 0.666$, $p = 0.03$; and 14–17 years: $r = 0.576$, $p = 0.031$).

4. Discussion

In this cross-sectional study, we assessed total serum IgA levels in a cohort of patients affected with JIA and age-matched controls. While IgA levels were comparable up to the age of 9 years between our cohorts of JIA children and controls, we instead observed a statistically significant difference between these two groups in patients aged 10–17 years: at this age, our cohort of JIA patients showed higher serum levels of IgA.

To our knowledge, this is the first controlled study assessing age-related IgA levels in such a relatively large cohort of JIA patients. Indeed, most of the previous studies in JIA patients actually aimed at investigating specific IgA and autoantibodies (for instance, those associated with Celiac Disease) and/or the association between IgA deficiency and this rheumatic disorder [19–22].

The only case-control study focused on immunoglobulins levels (including IgA) was published by Moradinejad et al. who investigated the association between IgAD and JIA among Iranian children. They found that all "the immunoglobulins levels in patients with JIA (IgM: 126.7 ± 57.2, IgG: 1182.3 ± 351 and IgA:169.3 ± 98) were significantly higher than their controls (IgM: 104 ± 52, IgG:802

Table 3
Correlation analysis between IgA levels and hematological, inflammatory, and disease activity parameters.

Age	JIA*	IgA	Covariation	CRP	ESR	HB	Plt.	WBC	Neutr.	Lymph.	JADAS-10
14–17 yrs	**All** (n = 64/75)	210.6 ± 98.9 mg/dl	r	−0.042	−0.117	−0.318	0.182	0.175	0.155	−0.247	0.359
			p	*0.740*	*0.357*	*0.010*	*0.149*	*0.166*	*0.222*	*0.049*	*0.005*
	oJIA (n = 26/30)	219.6 ± 115.6 mg/dl	r	0.263	***0.553***	−0.362	0.208	0.273	0.196	−0.265	0.442
			p	*0.195*	***0.003***	*0.070*	*0.308*	*0.178*	*0.336*	*0.191*	*0.045*
10–13 yrs	**All** (n = 70/77)	202.9 ± 112.6 mg/dl	r	0.291	0.419	−0.331	0.237	0.264	0.110	−0.130	0.260
			p	*0.015*	*0.000*	*0.005*	*0.049*	*0.027*	*0.366*	*0.283*	*0.041*
	oJIA (n = 42/46)	199.7 ± 88.5 mg/dl	r	0.573	**0.634**	−0.429	0.390	0.443	0.133	−0.106	**0.636**
			p	*0.000*	***0.000***	*0.005*	*0.011*	*0.003*	*0.401*	*0.504*	***0.000***
7–9 yrs	**All** (n = 50/61)	157.4 ± 87.1 mg/dl	r	0.257	0.471	−0.203	0.249	0.194	0.096	−0.089	0.151
			p	*0.071*	*0.001*	*0.157*	*0.082*	*0.176*	*0.506*	*0.215*	*0.296*
	oJIA (n = 31/38)	152.2 ± 73.6 mg/dl	r	0.369	**0.540**	−0.364	0.236	0.121	0.041	0.011	0.328
			p	*0.041*	***0.002***	*0.044*	*0.201*	*0.517*	*0.826*	*0.954*	*0.071*
4–6 yrs	**All** (n = 39/48)	117.8 ± 92.9 mg/dl	r	0.135	0.289	−0.582	0.426	−0.155	−0.097	0.108	0.248
			p	*0.414*	*0.074*	*0.000*	*0.007*	*0.345*	*0.556*	*0.513*	*0.133*
	oJIA (n = 30/36)	99.4 ± 48.5 mg/dl	r	0.298	**0.557**	−0.433	0.155	−0.271	0.182	−0.101	0.258
			p	*0.109*	***0.001***	*0.017*	*0.413*	*0.148*	*0.336*	*0.597*	*0.176*
1–3 yrs	**All** (n = 25/28)	76.0 ± 38.8 mg/dl	r	0.407	**0.760**	−0.492	0.400	0.399	0.094	−0.249	0.478
			p	*0.043*	***0.000***	*0.013*	*0.047*	*0.048*	*0.654*	*0.230*	*0.016*
	oJIA (n = 18/20)	76.7 ± 40.6 mg/dl	r	0.217	**0.812**	−0.428	0.460	0.399	−0.017	−0.253	0.485
			p	*0.386*	***0.000***	*0.076*	*0.055*	*0.101*	*0.947*	*0.312*	*0.041*

Table 4
Therapeutic overview of oJIA and non-oJIA patients (comparison between corresponding groups:‡p < 0.001; †p < 0.0001; ns = non-significant).

JIA patients	Age Classes					
	1–3 yrs	4–6 yrs	7–9 yrs	10–13 yrs	14–17 yrs	Total
Oligo-articular JIA	**20**	**36**	**38**	**46**	**30**	**170**
- *MTX*	18	26	29	32	15	120[ns]
	(90%)	*(72.2%)*	*(76.3%)*	*(69.6%)*	*(50%)*	*(70.6%)*
- *Biologics*	3	12	14	22	8	59[‡]
	(15%)	*(33.3%)*	*(36.8%)*	*(47.8%)*	*(26.7%)*	*(34.7%)*
- *Other immunosuppressors*	-	-	-	-	4	4[†]
	(0%)	*(0%)*	*(0%)*	*(0%)*	*(13.3%)*	*(2.3%)*
All other JIA subtypes	**8**	**12**	**23**	**31**	**45**	**119**
- *MTX*	3	7	21	24	31	86[ns]
	(37.5%)	*(58.3%)*	*(91.3%)*	*(77.4%)*	*(68.9%)*	*(72.3%)*
- *Biologics*	6	9	19	16	31	81[‡]
	(75%)	*(75%)*	*(82.6%)*	*(51.6%)*	*(68.9%)*	*(68.1%)*
- *Other immunosuppressors*	1	-	-	2	9	12[†]
	(12.5%)	*(0%)*	*(0%)*	*(6.5%)*	*(20%)*	*(10.1%)*

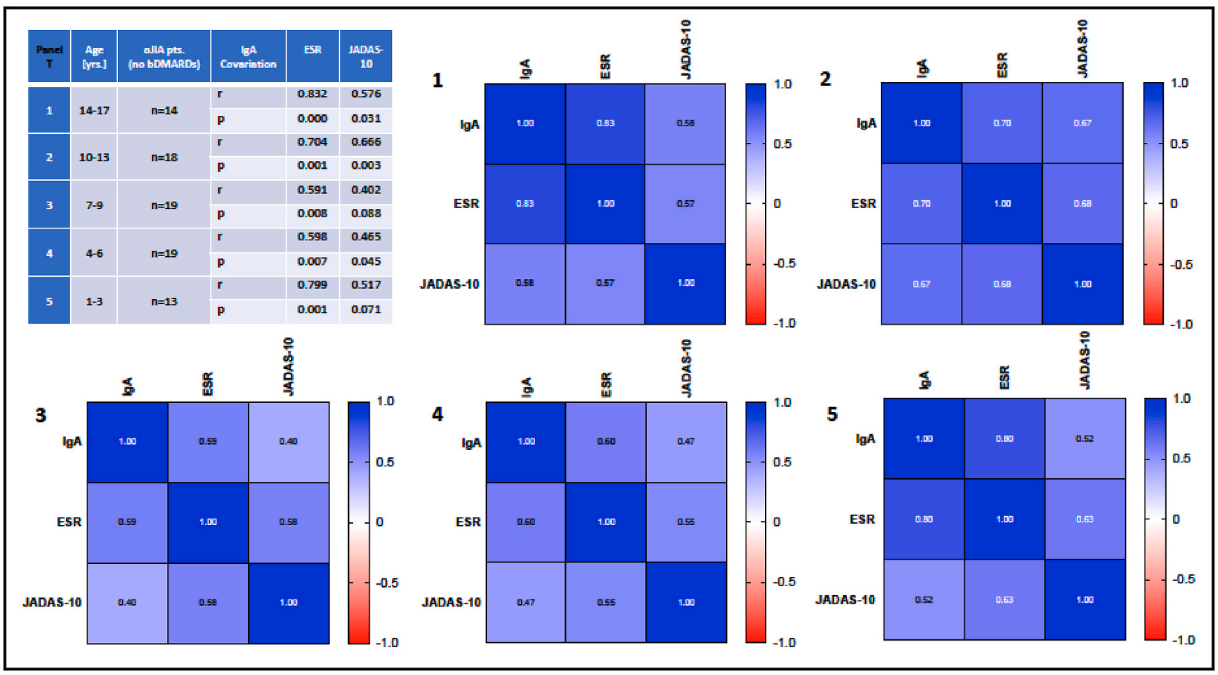

Fig. 2. Correlation analysis among total serum IgA levels, ESR and JADAS-10 score in the subgroup of oJIA patients free from bDMARDs and cDMARDs different from methotrexate (the table embedded inside the figure highlights the covariation and respective p-value between IgA levels and the other two parameters; the panels 1–5 graphically shows the covariation among all three parameters in each age class, as indicated in the embedded Panel T).

± 220 and IgA: 94.6 ± 47) ($p < 0.05$)." [23] However, they did not analyze the immunoglobulins according to the age class inside their pediatric cohorts. Indeed, it is well known that the IgA concentrations in children significantly increase with the age [24,25], and the absence of an age stratification and/or age matching can respectively impair the data interpretation and/or introduce some bias. In this study by Moradinejad et al. the mean of age of JIA patients (10.3 ± 3.9 years) was older than controls (9.1 ± 4.5 years), but such a difference was not statistically significant ($p = 0.076$); moreover, no specific correlation analysis was carried out, and the main general observation (not specific to IgA and/or JIA) was about children with growth failure, which showed higher immunoglobulin levels than those growing normally [23].

Other studies provided some data about serum IgA concentrations as a "collateral" information of research with different specific objectives. For instance, Stoll et al. analyzed total IgA and anti-tissue transglutaminase (tTG) IgA levels in 42 children with JIA and 10 "non-inflammatory control subjects". Here, the main conclusion was that total IgA and *anti*-tTG IgA levels resulted to be correlated, but no clear difference between JIA patients and controls was reported in terms of total serum IgA. Here, these authors also noticed significantly higher IgA levels in JIA patients with ERA phenotype, but a significant age difference was present among JIA patients

diagnosed with different subtypes (non-ERA patients: 6.9 ± 3.7 years; ERA patients: 12.9 ± 2.6 years) and control subjects (9.4 ± 3.6 years), which may have affected this comparison, as already mentioned [26]. More recently, Sahin et al. prospectively analyzed *anti*-tTG IgA in 96 JIA patients and also reported the total serum IgA levels in all JIA subtypes, in addition to the overall cohort; however, they did not report the IgA values according to the age classes and no specific analysis was done in this regard [27]. Avar-Aydin et al. investigated the incidence of allergy in JIA patients and, concomitantly, measured total serum IgA concentrations, as well. Again, no specific data were reported on this matter, except for the count of patients affected with hypogammaglobulinemia [28].

Very recently, Torres-Fernandez et al. specifically investigated IgA deficiency in JIA and reported a total IgA median value of 127 mg/dl (IQR 80–202 mg/dl) among those 172 JIA patients, in addition to identifying complete or partial IgA deficiency in 20% of them, overall. However, once again, no additional analysis of IgA levels according to age, JIA subtypes or other clinical/laboratory variables, was performed [29].

Therefore, unlike all these previous studies, we analyzed IgA levels in different age classes, which allowed us to perform a specific and age-matched comparison between JIA patients and control subjects. In our cohort of patients, we did not observe any difference in the frequency of low IgA levels consistent with the definition of IgAD, between JIA patients and controls, overall. However, an interesting finding was the fact that JIA patients aged 10–17 years showed significantly higher IgA levels than age-matched controls.

There are no previous observations like this in JIA patients, so far. However, Jorgensen et al. observed increased levels of IgA (>500 mg/dl) in 15.2% of their adult patients affected with rheumatoid arthritis (RA) [30]. As regards children, Yildiz et al. reported higher IgA levels in one patient affected with JIA (who concomitantly resulted to have IgG1 deficiency) [31].

Notably, the aforementioned paper by Jorgensen et al. also reported that their "hyper-IgA" RA patients showed increased ESR (in addition to increased incidence of distal interphalangeal arthritis, unilateral sacroiliitis and microscopic hematuria), compared to RA patients with normal IgA levels [30]. This observation is somehow consistent with our analysis correlating IgA levels in oJIA patients with ESR, which may be related to the presence of chronic/persistent inflammation, especially in the rheumatic setting [32,33].

Although ESR values are known to increase according to the age in adulthood (especially in elderly patients), no significant changes in ESR normal range is described over the pediatric age, except for lower values in newborns [34], which are not included in our study population, anyway. Therefore, one might speculate that IgA levels could be affected by the inflammatory status in terms of control and/or duration. Some association between serum markers of the humoral immune system and inflammation was observed in the very recent Swedish AMORIS study investigating this aspect in 5513 individuals; however, even though several inflammation markers were considered in this study (such as CRP, albumin, haptoglobin, WBC, iron, and total iron-binding capacity), ESR was not included [35]. Previous research also suggested that higher IgA levels could be observed in a wide range of chronic inflammatory disorders and/or a correlate with disease activity indexes [36–38].

Interestingly, such a moderate, but significant, covariation between serum IgA levels and ESR was observed only in oJIA patients and not in other JIA subtypes or all JIA patients overall. This mismatch between oJIA and other JIA subtypes in general may be due to other factors, including the effect by the maintenance therapy [39,40], which was significantly different between oJIA and non-oJIA patients: indeed, the latter category of patients was much more exposed to biological drugs and cDMARDs other than methotrexate. In this regard, in those oJIA patients not exposed to bDMARDs, such a covariation (between IgA levels and ESR) was stronger and, notably, some moderate and positive correlation was observed with JADAS-10 as well.

Of course, this study has several limitations. In addition to the observational nature of this cross-sectional study and the heterogeneity of the study population, most patients were under maintenance therapy and non-oJIA subtypes were less represented, according to their general epidemiological relative proportions inside JIA population. Moreover, since all the clinical and laboratory data were secondary, except for the measurement of total serum IgA, some parameters were not available for all patients; unfortunately, the limited funds did not allow to concomitantly measure IgM and IgG; finally, the sample size was based on the voluntary participation of eligible patients and their guardians, without any preliminary power analysis for sample size determination.

In conclusion, in our cohort of JIA patients, total serum IgA levels were not reduced and were actually increased in adolescents compared to controls. Larger studies are needed to confirm this finding, which cannot be certainly explained based on the available data in this study, even though JIA disease control and/or chronic inflammation may be implicated to some extent.

Author contributions statement

DP conceived and designed the experiments; DP, DA, KD, ZA, ZM, MA, LH, and DZ analyzed and interpreted data; KN, NB, KK, and MT performed the experiments; DP, DA, and KD contributed to reagents, materials, analysis tools or data; DP wrote the paper. All authors have read and agreed to the published version of the manuscript.

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Data availability statement

As regards the possibility to publicly share the full dataset (in addition to the extracted and aggregated data), there are some ethical restrictions, according to the NU-IREC approval and hospital policies. However, the anonymized dataset could be available upon request to be sent to the corresponding author.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dimitri Poddighe reports financial support was provided by Nazarbayev University School of Medicine. Dimitri Poddighe reports a relationship with Nazarbayev University School of Medicine that includes: employment.

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