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Serum Immunoglobulin Concentrations in Juvenile Idiopathic Arthritis Cases during Active and Inactive Disease States

Sajib Muhammad Rayhan[1], Kamrul Laila[2], Shahana A. Rahman[3]

[1]Consultant (Paediatrics), Kalkini Upazila Health Complex, Dhaka, Bangladesh
[2]Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
[3]Department of Paediatrics (on PRL) Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
Email: sajibrayhan@yahoo.com, drlaila28@gmail.com, shahana2pd@yahoo.com

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Abstract

Background: Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children. Both the humoral and cell mediated immunities are involved in the pathogenesis of JIA. It is reported that overall immunoglobulin levels in JIA patients are significantly higher than their control during the active state of disease. **Methodology:** This prospective observational study was conducted over a period of 18 months All the newly diagnosed oligo-articular and poly-articular JIA patients having active disease were included by purposive sampling. Data were collected by a semi-structured predesigned questionnaire. **Result:** Most of the study subjects (57.6%) belonged to age group > 3 - 9 years. Oligo JIA was diagnosed in 66.7% and poly JIA in 33.3% of JIA children. The difference in mean (±SD) ESR (33.52 ± 21.29 and 15.09 ± 7.71 mm in 1st hour) at active and inactive states was highly significant. Mean (±SD) difference of IgG, IgM and IgA in active and inactive states of disease were highly significant. **Conclusion:** Higher and abnormal levels of immunoglobulin (IgG, IgM, and IgA) were present among JIA patients in active disease state which became normal during inactive disease state after treatment.

Keywords

JIA, Oligoarticular JIA, Polyarticular JIA, Immunoglobulins, Acitive Disease, Inactive Disease

1. Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in

children. The global prevalence of JIA has been estimated to range from 3.8 to 400/100,000 with an incidence of 1.6 to 23/100,000 [1]. In the United Kingdom, the age-standardized prevalence rate in 2018 was 43.5 per 100,000 [2]. The exact incidence and prevalence of JIA is not known in our country. A pilot study in a semi-urban area of Bangladesh showed the prevalence of JIA as 60.5 per 100,000 [3].

JIA is an immune mediated disease. Alterations of the immune system have been documented in JIA [4]. Both the humoral and cell mediated immunities are involved in the pathogenesis of JIA. T lymphocytes play a central role in the release of proinflamatory cytokines (TNF, IL1 and IL6). Evidences of abnormalities in the humoral immune system include increased presence of autoantibodies (especially antinuclear antibodies), increased serum immunoglobulins, presence of circulating immune complexes and complement activation [4]. The association of RF (Rheumatoid factor-antibodies reactive to IgG) with the disease also suggests an immune mechanism. It is reported that overall immunoglobulin levels in JIA patients are significantly higher than their control and JIA patients with growth failure had higher IgM, IgA and IgG levels in comparison with patients without growth failure [5]. Immunodeficiency states such as selective IgA deficiency and hypogammaglobulinemia are also reported as statistically more frequent in children with chronic arthritis in [6].

Initiation of the JIA pathophysiological cascade includes abnormal activation of T-cells, B-cells, natural killer (NK) cells, dendritic cells (DC), macrophages and neutrophils and the production of pro-inflammatory mediators that cause joint destruction and systemic complications. Oligoarticular and polyarticular JIA are characterized by auto-reactive antigen-specific T-cells and high titres of autoantibodies, and typically show strong associations with MHC class II alleles. Breakdown of immunologic self-tolerance involves MHC class II alleles suggesting a pivotal role for CD4+ T helper (Th) cells [7].

Inflammation is considered to be a consequence of a disrupted balance between pro-inflammatory Th1/Th17 and anti-inflammatory regulatory T-cells (Treg) [8]. Systemic JIA (sJIA) cases are suggested to have an auto inflammatory pathology with different pathogenesis [9]. In enthesitis related arthritis (ERA) there is more genetic susceptibility rather than immunological predisposition. The pathogenesis of ERA is also different from other types of JIA [10].

The goal of treatment in JIA patients is to bring the disease activity into remission. When the patient has inactive disease state, the inflammatory process is also stopped and immunological markers come down to normal concentration [4].

No study so far has been done to measure immunoglobulin (IgG, IgM, and IgA) levels in JIA patients in our country. This study was carried out with the objective of assessing the immunoglobulin levels and comparing these levels during active and inactive states of oligo and polyarticular JIA patients in a tertiary care hospital in Bangladesh.

2. Materials AND Methods

It was a prospective observational study, conducted in a pediatric rheumatology clinic, Department of Pediatrics and Department of Microbiology and Immunology, Bangabandhu Sheikh Mujib Medical University (BSMMU).

The study period was 18 months (From January 2016 to June 2017). All the newly diagnosed oligo-articular and poly-articular juvenile idiopathic arthritis patients, having active disease attending paediatric rheumatology clinic and inpatient department of paediatrics, BSMMU during the study period were included by purposive sampling.

Because of different pathogenesis, systemic onset JIA (sJIA) and ERA cases were not included in this study.

JIA patients, not having active disease or in remission and patients unwilling to give consent were excluded from the study. JIA patients likely to have confounding factors including severe malnutrition, steroid therapy, immunosuppressive therapy or chronic co-morbidities were excluded from the study. Ethical clearance was taken from the Institutional Review Board (IRB) of BSMMU before starting the study.

Data were collected by a semi-structured predesigned questionnaire developed in Bangla (Bengali). Prior pre-testing was done on 10 cases to test the reliability and validity. Later on, the questionnaire was translated into English by competent persons. Both the Bangla and English versions were used according to requirements but data entry and calculation were done in English.

The patients and their parents were informed about the study design and its objectives. They were explained that there would be no physical or social risk for the participants except minor pain during venipuncture. They were also informed about the freedom to participate or not to participate at any time. No incentive was given for participation.

2.1. Study Procedure

Sample Size calculation

As an observational study the sample size was calculated in following manner:

sample size $n = \left[\left(z_\alpha + z_\beta\right)^2 \times \left(\delta_1^2 + \delta_2^2\right)\right] \Big/ \left(\mu_1 - \mu_2\right)^2$ [11].

z_α = Confidence level 95% = 1.96

z_β = Standard normal distribution of a definite power; 0.85

μ_1= Mean of one group; 1790

μ_2= Mean of other group; 1570

δ_1 = SD of one group; 535

δ_2 = SD of other group; 360

$n = \left\{\left(1.96 + 0.85\right)^2 \times \left(535^2 + 360^2\right)\right\} \Big/ \left(1790 - 1570\right)^2 = 68$

A total of consecutive 68 newly diagnosed cases of poly and oligo-JIA cases fulfilling inclusion criteria were included in the study. But two poly-JIA patients did not come for regular follow-up. So analysis of 66 patients was done in the

study. After diagnosis of JIA cases in pediatric rheumatology follow up clinic, the pre-designed questionnaire was completed for each patient by interviewing them or their parents after taking their written consent. Information was also obtained from their medical records. Variables included patients' characteristics including age (in years), gender, diagnosis (sub-types), and duration of disease (in months) and biochemical parameters of blood sample during active (at initial visit) and inactive diseases state (at 6 months, 9 months or 12 months follow up, whenever the JIA cases became inactive). All the JIA patients were treated by the pediatric rheumatologists according to standard protocol with the objective of bringing the disease into an inactive state. Diseases activity was measured by Wallace criteria 2004 [12]. Follow up of patients was done at 3, 6, 9 and 12 months.

2.2. Collection of Blood

With all aseptic precautions 2 ml venous blood sample was drawn from the ante-cubital vein. The blood sample was transferred immediately into a coded test tube without any anticoagulant agents and kept for investigation in the Microbiology and Immunology department and preserved in ultra-freezer at minus 20 degrees centigrade until the analysis.

Quantitative measurements of serum immunoglobulins IgG, IgA and IgM were done via nephelometry in the Department of microbiology and immunology, BSMMU. All the investigations were done at the time of diagnosis during active diseases state and again repeated when disease state became inactive during follow up at 6 months, 9 months or 12 months.

All the investigation result of immunoglobulin was given in gm/L from the Department of Microbiology and Immunology, BSMMU. As the standard reference value is given in mg/dl, the supplied results were converted to mg/dL. In addition as the value was given in the adult range, the values were also converted into pediatric range by using the software provided by:
http://www.endmemo.com/medical/unitconvert/Immunoglobulin_G.php.

2.3. Normal Immunoglobulin Concentration in Adult [13]

IgG (gm/lt)	IgM (gm/lt)	IgA (gm/lt)
7 - 16	0.4 - 2.3	0.7 - 4.0

Conversion of immunoglobulin concentration from reference range was done in following way:

Age 1 - 3 years: 453 - 916 mg/dL

Conversion to gm/L, dividing by 100: 4.53 - 9.16 gm/L

http://www.endmemo.com/medical/unitconvert/Immunoglobulin_G.php reference

All the parameters were compared between active and inactive diseases state. All statistical calculations were done using the statistical software SPSS 21.0. The

Chi-square test or t-test was applied to evaluate the association between the variables when indicated. The results were presented in Tables, figures & diagrams. P-value less than 0.05 were considered as significant at a 95% confidence interval for the correlation.

3. Result

Among the total 66 JIA children, 39.4% were male and 60.6% were female. Mean (±SD) age was 7.97 ± 3.72 (range 2 - 14) years. Most of the study subjects (57.6%) belonged to age group > 3 - 9 years, followed by > 9 years (36.4%). Oligo-JIA was diagnosed in 66.7% and poly-JIA in 33.3% of JIA children (Table 1).

Mean (±SD) platelet count was 413.45 ± 135.46 in the active state and 350.97 ± 100.34 10^9/L in the inactive state, respectively. The difference was significant ($P < 0.05$). The difference in mean (±SD) ESR at active state (33.52 ± 21.29) and inactive state (15.09 ± 7.71 mm in 1st hour) was also highly significant (Table 2).

Table 3 shows immunoglobulin concentrations in active and inactive states of all JIA patients (n = 66). Mean (±SD) difference of IgG at active state (13.04 ± 4.41) and inactive state (9.88 ± 2.31 g/L) was highly significant ($P < 0.001$). Mean (±SD) difference of IgM at active state (3.25 ± 1.80) and inactive state (1.82 ± 0.88 g/L) of disease was highly significant ($P < 0.001$). Mean (±SD) difference of IgA was also highly significant (Table 3).

Figure 1 shows the status of immunoglobulin concentrations of oligo-JIA patients in an active and inactive state of disease (n = 44). Mean (±SD) IgG was 11.95 ± 4.58 in the active state and 9.48 ± 2.58 g/L in inactive state of disease. The difference was highly significant ($P < 0.01$). The mean difference in IgM concentration between active and inactive disease was also highly significant ($P < 0.001$). Mean (±SD) IgA was 3.03 ± 1.36 in an active state and 1.31 ± 0.54 g/L in inactive state of the disease and the difference was highly significant ($P < 0.001$).

Figure 2 shows status of immunoglobulin concentrations of poly-JIA patients

Table 1. Gender, age and types of JIA among the study population (n = 66).

Parameters	Mean ± SD	No. (%)
Gender		
Male		26 (39.4)
Female		40 (60.6)
Age (in years)	7.97 ± 3.72	
1 - 3		4 (6.1)
> 3 - 6		20 (30.30)
> 6 - 9		18 (27.27)
>9		24 (36.4)
Diagnosis of JIA		
Oligo-JIA		44 (66.7)
Poly-JIA		22 (33.3)

Table 2. Laboratory parameters of JIA cases in active and inactive states of patients (n = 66).

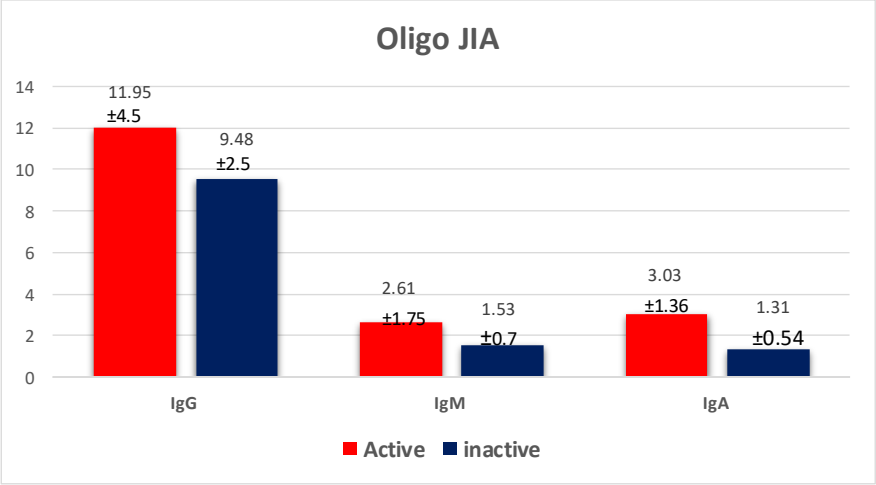
Parameter	Active state	Inactive state	*P value*
(Mean ± SD)	(Mean ± SD)		
Hb (g/dl)	10.93 ± 1.69	11.36 ± 0.93	0.098^{ns}
TC (10^9/L)	7.00 ± 3.22	9.06 ± 2.74	0.981^{ns}
WBC DC-N (%)	55.82 ± 14.55	55.58 ± 10.41	0.925^{ns}
WBC DC-L (%)	36.85 ± 14.71	32.36 ± 12.07	0.160^{ns}
Platelet (10^9/L)	413.45 ± 135.46	350.97 ± 100.34	0.021*
ESR (1st hr)	33.52 ± 21.29	15.09 ± 7.71	0.0001***

Paired student's "t" test.
ns = Not significant.
* = Significant at P < 0.05.
*** = Significant at P < 0.001.

Table 3. Status of immunoglobulin concentrations in active and inactive state of disease in JIA patients (n = 66).

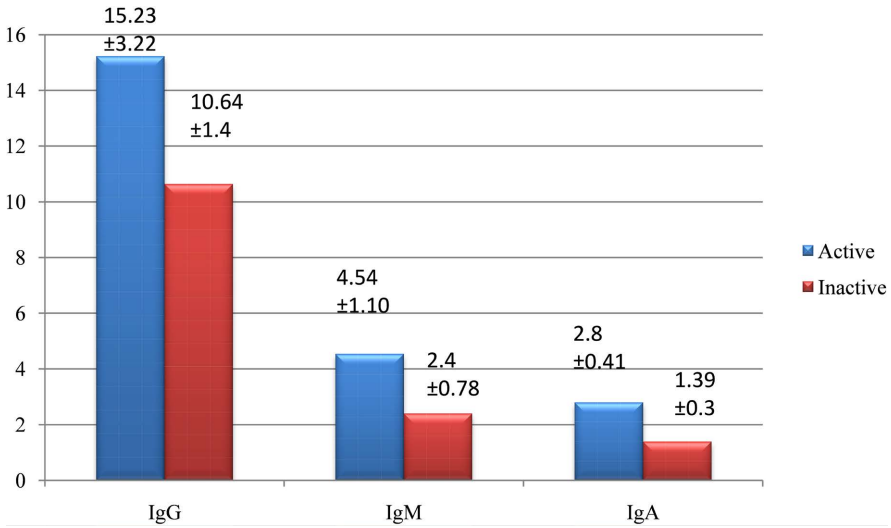
Parameter	Active state	Inactive state	*P value*
(Mean ± SD)	(Mean ± SD)		
IgG (g/L)	13.04 ± 4.41	9.88 ± 2.31	0.0001***
IgM (g/L)	3.25 ± 1.80	1.82 ± 0.88	0.0001***
IgA (g/L)	3.29 ± 1.18	1.34 ± 0.47	0.0001***

Paired student's "t" test.
*** = Significant at P < 0.001.



Paired student's "t" test; ** = Significant at P < 0.01; *** = Significant at P < 0.001.

Figure 1. Status of immunoglobulin concentrations of oligo-JIA in active and inactive state of disease (n = 44).



Paired student's "t" test; *** = Significant at P < 0.001.

Figure 2. Status of immunoglobulin concentrations of poly-JIA patients in active and inactive state of disease (n = 22).

in active and inactive state of disease (n = 22). Differences of mean IgG, IgM and IgA between active and inactive state of disease were highly significant (P < 0.001).

4. Discussion

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease affecting hundreds of thousands of children worldwide. Advances in our understanding of the pathogenesis of JIA over the last two decades have revolutionized therapy, reduced morbidity, and improved the quality of life for children with JIA [14]. Although the disease's etiology is unknown, disturbances in innate and adaptive immune responses have been implicated. B cells may have important roles in JIA pathogenesis through autoantibody production, antigen presentation, cytokine release and/or T cell activation [15].

Globally, approximately 3 million children and young adults are estimated to suffer from JIA. Girls were consistently found to be at a higher risk than boys, and oligoarticular subtype was found to be predominant [1].

Hematologic abnormalities generally reflect the extent of the inflammatory disease. Useful laboratory investigations include blood count (CBC) and inflammatory markers like erythrocyte sedimentation rate (ESR) [16]. In general, ESR is a useful measure of active disease in a child with JIA [12]. One of the effects of pro-inflammatory cytokines produced in response to systemic inflammation in the liver is megakaryocyte stimulation and thus increases in the number of platelets in response to inflammation. This results in the production of larger and more reactive platelets [17]. In our study cases, ESR and platelet count were significantly higher in active diseases state and became normal in inactive disease states (p value < 0.05). These findings were similar to previous studies [18].

In our center, another study was conducted among JIA patients showing, higher mean neutrophil count and platelet count during the active state of the disease. Mean ESR and CRP were raised in all JIA patients at the active state which explains the strong association of CRP and ESR with JIA disease activity [19].

JIA is a complex autoimmune disease and its exact etiology is still unknown. But it is an established fact that a combination of genetic susceptibility and unknown environmental triggers leads to immune imbalance. T lymphocytes play a central role in the release of proinflamatory cytokines (TNF, IL1 and IL6). Evidence for abnormalities in the humoral immune system includes the increased presence of autoantibodies (especially antinuclear antibodies), increased serum immunoglobulins, the presence of circulating immune complexes, complement activation and association of RF (Rheumatoid factor-antibodies reactive to IgG) [4].

The ultimate goal of treatment in JIA patients is to achieve remission, i.e. complete suppression of disease activity. When the active disease process is stopped and the patient has an inactive disease state, the inflammatory process is also stopped and immunological markers come down to normal concentration [20].

In the present study, the concentrations of the serum immunoglobulins IgG, IgM, and IgA were determined in 66 JIA patients, where abnormalities (much higher concentration) of these Immunoglobulins were found in active state. These results were similar to previous studies [5] [21]. In the study done by Veys *et al.* it was found that there was the elevation of IgG and IgA levels but IgM level was normal in JIA cases in an active disease state [11]. Some studies also found elevations in serum IgG and selective depressions in serum IgA levels in active disease states [22].

In the present study, significantly higher concentrations of IgG, IgA, and IgM were found in an active disease state, which became lower and normal during an inactive state. A study done by Rackham OJ *et al.* had shown similar results [23]. But a study done by Torre *et al.* found different results where, immunoglobulin concentration was low to normal range in inactive state but IgA concentration were still high in a number of patients [24].

When the total JIA cases were subdivided into oligo articular and poly articular JIA group, it was found that among 44 oligo JIA patients, all the three immunoglobulin (IgG, IgM and IgA) concentration was significantly higher in active diseases state. These findings were comparable with previous studies [23] [24].

Similarly, among 22 polyarticular JIA patients, it was found that the difference in IgG, IgM, and IgA concentration between active and inactive disease states was highly significant ($P < 0.001$) which supports the findings of Rackham OJ *et al.* in 2002. However a study done by Davies K *et al.* showed that there was a decrease concentration of IgA in poly articular JIA in active disease state [25].

In the present study IgG, IgM, IgA concentration significantly fell and became

normal during inactive state of disease. Rackham OJ *et al.* found similar results whwre IgG, IgM and IgA concentration significantly fall in inactive disease state [23]. Torre ID *et al.* also found similar result [24]. It was expected that majority of the patients have abnormal concentration of immunoglobulins at presentation during the initial active diseases state which would become normal after treatment during inactive disease state. Our study results fulfilled the expectations. Determination of serum immunoglobulin concentration is of potential importance for understanding the pathogenesis involved in autoimmune and inflammatory disorders [26].

5. Conclusion

The study concluded that significantly higher and abnormal levels of immunoglobulin (IgG, IgM, and IgA) were present among JIA patients in active disease state which became normal during inactive disease state after treatment. Clinical implications of Immunoglobulin levels could be understood from this study. Measuring immunoglobulin levels may guide the disease progression or improvement and decisions regarding treatment.

6. Recommendations

From the results and observation of this study, following recommendations may be made:

1) Further multicenter study should be done with larger sample size.

2) Immunoglobulin concentration value should be provided for pediatric age range from the Department of microbiology and immunology where investigations are done.

7. Limitations of the Study

It was a single center study with short study period.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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