Comparison of Serum Immunoglobulin (IgG, IgM and IgA) Concentration During Active and Inactive Disease States in Patients with Juvenile Idiopathic Arthritis

Rayhan SM[1], Akter M[2],Islam I[3]

[1]Dr. Sajib Muhammad Rayhan, Residential Medical officer, Sonargaon Upazila Health complex, Narayanganj, Bangladesh. Email: sajibrayhan@yahoo.com, Orcid ID: 0000-0003-2153-1284
[2]Dr. MahfuzaAkter, Registrar, Department of Ophthalmology, Mugda Medical College and Hospital, Dhaka, Bangladesh. Email: rummyrayhan@yahoo.com, Orcid ID: 0000-0001-7757-2291
[3]Dr. Md. Imnul Islam, Professor, Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. Email: imon27@gmail.com, Orcid ID: 0000-0003-0092-859X

Abstract

Background: The majority of patients with juvenile idiopathic arthritis (JIA), a prevalent rheumatological condition, are predicted to have abnormal immunoglobulin concentrations upon presentation during the early active disease state, which would normalize after treatment during the inactive disease state. Immunoglobulin concentration can therefore be changed due to Immunomoduler drugs.**Objectives:**The objective of this study is to investigate the serum levels of IgG, IgM, and IgA in JIA patients in order to better understand the serum immunoglobulin concentration throughout active and inactive disease states.**Methods:** This is an observational study. The study used to be carried out in the admitted patient's Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Bangladesh from October 2015 to March 2017.The medical records and radiographs of 33 patients who participated in this study were the source of the data. Statistical analysis of the results was previously obtained using window-based software created with Statistical Packages for Social Sciences (SPSS-24).**Results:** The study comprised 33 JIA patients with ages ranging from 1 to >9 years old. The active states of IgG (g/L), IgM (g/L), and IgA (g/L) in this instance were 13.04±4.41, 3.25±1.80 and 3.29±1.18 respectively, according to Parameter. Additionally, the inactive states of IgG, IgM, and IgA were 9.88±2.31, 1.82±0.88 and 1.34±0.47, respectively. **Conclusions:**The study concluded that high and abnormal levels of immunoglobulin (IgG, IgM, and IgA) is present among JIA patient in active disease state which became normal in inactive state.

Keywords: Juvenile Idiopathic Arthritis (JIA); Rheumatological; Immunoglobulins; Oligoarticular; Chronic anterior uveitis; Polyarticular.
Corresponding Author: Dr. Sajib Muhammad Rayhan, Residential Medical officer, Sonargaon Upazila Health complex, Narayanganj, Bangladesh. Email: sajibrayhan@yahoo.com,

Introduction:

A chronic inflammatory condition known as juvenile idiopathic arthritis (JIA) affects hundreds of thousands of children around the worldunder the age of 16 who develops arthritis and lasts for at least six weeks is said to have juvenile idiopathic arthritis (JIA).[1] The term "JIA" refers to

seven different types of juvenile arthritis, each of which has a unique pathophysiology, hereditary factors, and clinical presentation.[2]

Alterations of Immune system have been documented in JIA.[3]Immunoglobulins (Igs), which are glycoprotein molecules known as antibodies (Abs), are produced in response to foreign substances and enter the body or immunogens (viruses, bacteria, or toxins, etc.). [4] They bind to these immunogens and form antigen-antibody complexes, which lead to the removal of the immunogen (Ag) and protection of the infected host.[5]

Both the humoral and cell mediated immunities are involved inpathogenesis of JIA. T lymphocytes play a central role in the release of proinflammatory cytokines (TNF, IL1 and IL6). Evidence for abnormalities in the humoral immune system include theincreased presence of autoantibodies (especially antinuclear antibodies), increased serumimmunoglobulins, the presence of circulating immune complexes and complement activation.Both Anti-nuclear antibody (ANA) and Rheumatoid factor (RF) seropositivity can occur inassociation with transient events, such as viral infection in JIA.[6] Paradoxically, immunodeficiency states suchas selective IgA deficiency andhypogammaglobulinemia are statistically more frequent inchildren with chronic arthritis.[7] It is reported that over all Immunoglobulin levels in JIApatients are significantly higher than their control. JIA patients with growth failure had higherIgM, IgA and IgG levels in comparison with patients without growth failure. Immunodeficiency,hypogammaglobulinemia and also hypergammaglobulinemia are more frequent in JIA patient.[8]

Whatever may be the initiating stimulus, JIA is characterized by persistent cellular activation, autoimmunity and presence of immune complexes. The pathogenesis of systemic onset of JIA (sJIA) is different from oligoarticular and polyarticular type. In sJIA,autoinflammatory response is more responsible than immunological process.[9]

The ultimate goal of treatment in juvenile idiopathic arthritis patient is remission, i.e., complete suppression of disease activity. When the active disease process is stopped and patient has inactive diseases state, the inflammatory process is also stopped and immunological markers come down to normal concentration.This study aims to examine the serum concentration of IgG, IgM, and IgA in patients with JIA to better understand the serum immunoglobulin concentration during active and passive disease phases.

Methodology:

This is an observational study. The study used to be carried out in the admitted patient's Department of pediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Bangladesh. In Bangladesh for the duration of the period from October 2015 to March 2017. This study was carried out on 33 patients the find out about the population including male and female patients in the Department ofPaediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Bangladesh.The medical Pediatricians,Neonatologist and the surgeon were primarily involved in the decision-making process. The choice of treatment was made by the patient after a full discussion with the multidisciplinary team consisting of pediatricians, neonatologists and pediatric endocrinologists and surgeons. The data for this study was gathered from radiographs and medical records of the individuals. Following collection, the data were examined and cleaned before being edited, compiled, coded, and categorized in accordance with the objectives and variables in order to identify errors and ensure consistency, relevance, and quality control.

The data were then input into a computer for analysis.A window-based computer program created with Statistical Packages for Social Sciences was utilized to obtain statistical analysis of the results (SPSS-24).

Results:

A total of 33 JIA patients aged between 1 and >9 years old were included in the study. Here, according to age distribution, 2 (6.1%) were between the ages of 1 and 3, 10 (30.30%) were between the ages of 3 and 6, 9 (27.27%) were between the ages of 6 and 9, and 12 (36.4%) were over 9. In terms of gender, 13 (39.4%) men and 20 (60.6%) women were present. 22 (66.7%) of the JIA diagnoses were Oligo and 11 (33.3%) were Poly. IgG, IgM, and IgA had active states of 13.04±4.41, 3.25±1.80 and 3.29±1.18 respectively. IgG (g/L), IgM (g/L), and IgA (g/L) were in an inactive condition and had respective values of 9.88±2.31, 1.82±0.88 and 1.34±0.47 respectively. IgG concentrations in active and inactive state of disease, respectively was normal in 19 (57.6%) and 32 (97%), and abnormal in 14 (42.5%) and 1 (3%) JIA patient (P<0.001), IgM concentrations in active and inactive state of disease, respectively was normal in 13 (39.4%) and 33 (100%), and abnormal in 20 (60.6%) and none patients (P<0.001). ang IgA concentrations in active and inactive state of disease, respectively was normal in 6 (18.2%) and 31 (93.9%), and abnormal in 27 (81.8%) and 2 (6.1%) patients (P<0.001).

Table-I: Distribution of the patients according to Diagnosis of JIA

Diagnosis of JIA	n=33	%
Oligo JIA	22	66.7
Poly JIA	11	33.3

Table I demonstrated the patients according to Diagnosis of JIA of 33 Patients. Here according to Diagnosis of JIA, 22(66.7%) were Oligo and 11(33.3%) were Poly.

Table-II: Status of immunoglobulin concentrations in active and inactive state of disease in JIA patients (n=33)

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

Table II demonstrated Status of immunoglobulin concentrations in active and inactive state of disease in JIA patients (n=33). Here according to Parameter, Active state of IgG (g/L), IgM (g/L) and IgA (g/L) were 13.04±4.41, 3.25±1.80 and 3.29±1.18 respectively. And Inactive state were of IgG (g/L), IgM (g/L) and IgA (g/L) were 9.88±2.31, 1.82±0.88 and 1.34±0.47 respectively. The mean difference was highly significant (p<0.001).

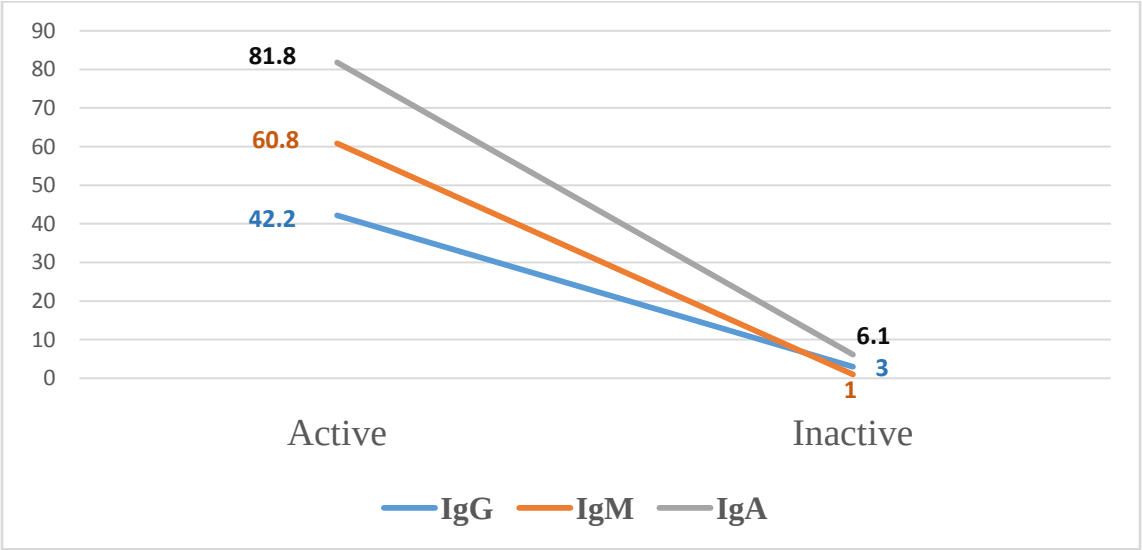

Figure I: Abnormal levels of immunoglobulin in JIA patients in active and inactive state of disease (n=33).

Figure Ishows status of abnormal immunoglobulin concentrations in active and inactive state of all JIA patient (n=33).Here, AbnormalIgG concentrations in active state was in 14 (42.5%) and in inactive state was in 1 (3%) JIA patient (P<0.001). Abnormal IgM concentrations in active state was in 20 (60.6%) and inactive state was in none patients (P<0.001). Abnormal IgA concentrations in active state was in 27 (81.8%) and in inactive state was in 2 (6.1%) patients (P<0.001).

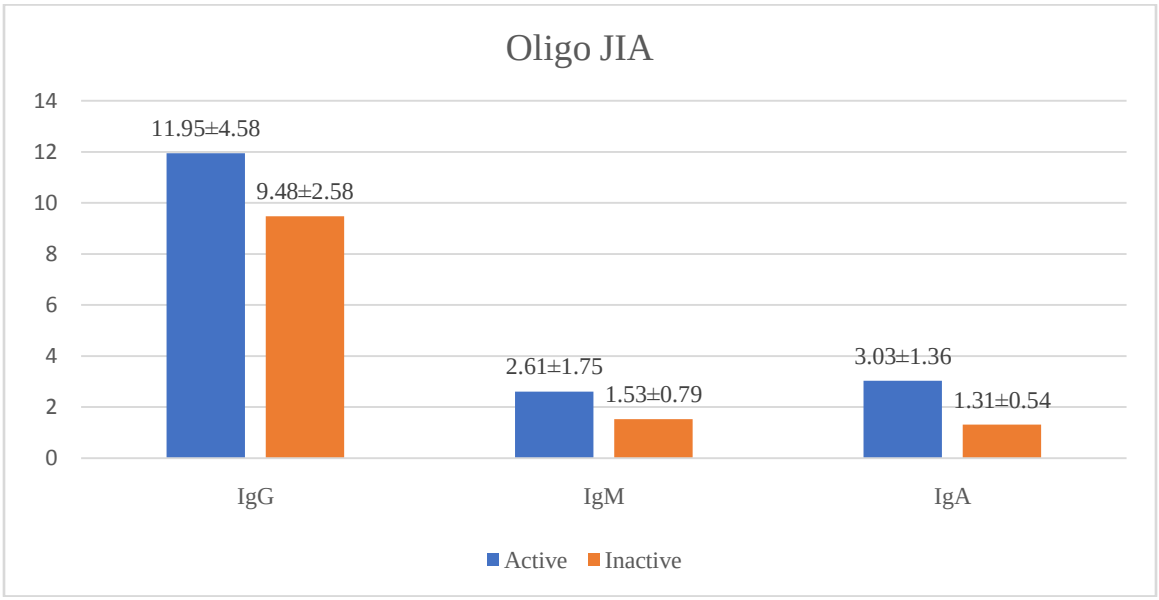

Figure II: State of immunoglobulin concentrations of oligo-JIA in active and inactive state of disease (n=22).

Mean (±SD) IgG was 11.95±4.58 and 9.48±2.58 g/L in active and inactive state of disease, respectively. The difference was highly significant (P<0.01). Mean (±SD) IgM was 2.61±1.75 and 1.53±0.79 g/L in active and inactive state of disease, respectively. The mean difference was highly significant (P<0.001). Mean (±SD) IgA was 3.03±1.36 and 1.31±0.54 g/L in active and inactive state of disease, respectively. The mean difference was highly significant (P<0.001).

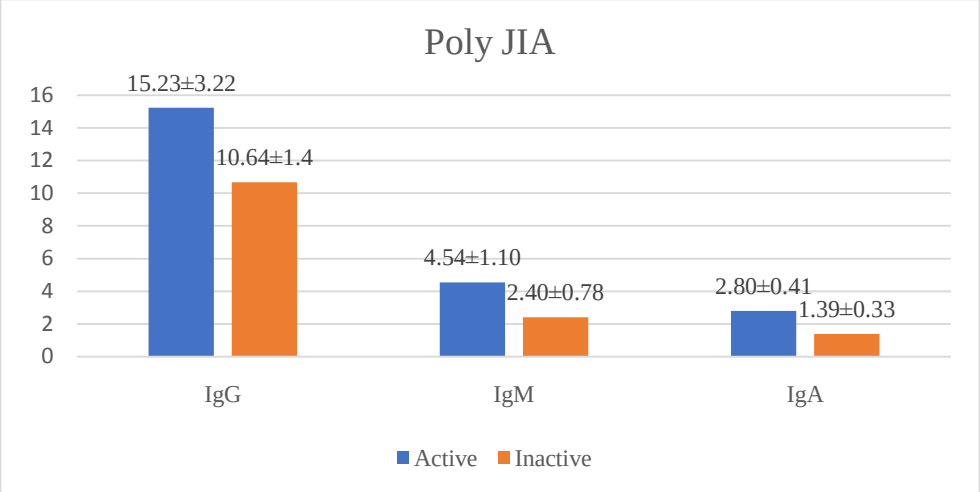

Figure III:State of immunoglobulin concentrations of poly-JIA in active and inactive state of disease (n=22).

Mean (±SD) IgG was 15.23±3.22 and 10.68±1.40 g/L in active and inactive state of disease,respectively. The difference was highly significant (P<0.001).Mean (±SD) IgM was 4.54±1.10 and 2.40±0.78 g/L in active and inactive state of disease, respectively. The mean difference was highly significant (P<0.001).Mean (±SD) IgA was 2.80±0.41 and 1.39±0.33 g/L in active and inactive state of disease, respectively. The difference was highly significant (P<0.001).

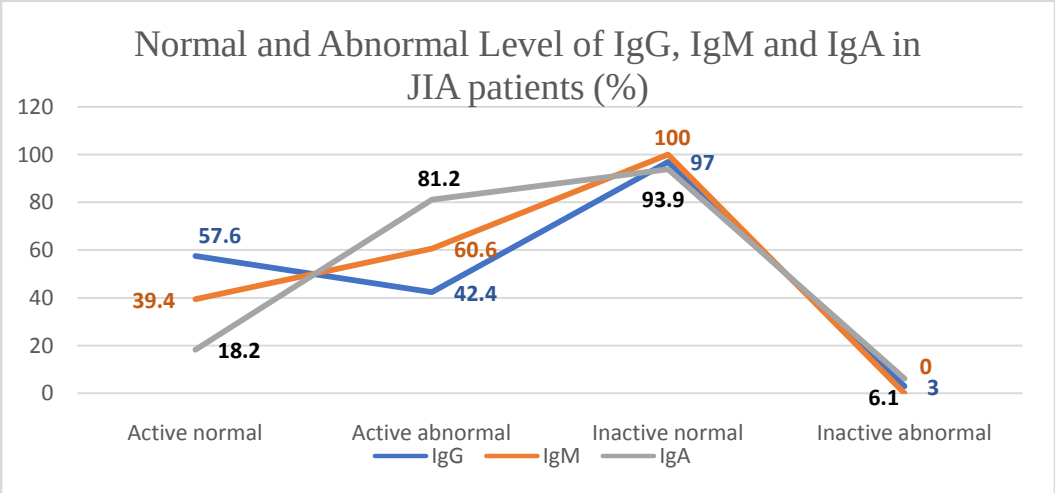

Figure IV: Normal and Abnormal Level of IgG, IgM and IgA in JIA patients (n=33)

Figure shows IgG concentrations in active and inactive state of disease, respectively was normal in 19 (57.6%) and 32 (97%), and abnormal in 14 (42.5%) and 1 (3%) JIA patient (P<0.001), IgM concentrations in active and inactive state of disease, respectively was normal in 13 (39.4%) and 33 (100%), and abnormal in 20 (60.6%) and none patients (P<0.001). ang IgA concentrations in active and inactive state of disease, respectively was normal in 6 (18.2%) and 31 (93.9%), and abnormal in 27 (81.8%) and 2 (6.1%) patients (P<0.001).

DISCUSSION

Juvenile idiopathic arthritis (JIA) is a chronic systemic autoimmune disease of widely varying expression and severity. [10] and itsetiopathogenesis continues to be a challenge. [11] Many other recognized or yet unrecognized autoantibody systems are identified as immunological abnormalities. [12]In our study, according to age of 33 Patients aged 1 to 9 years and according to gender 13(39.4%) were Male and 20(60.6%) were Female.

In our study among the patient of oligo articular and poly articular JIA, ESR and platelet count were higher in active diseases state and become normal in inactive diseases which were statistically significant (p value < 0.05). These findings were similar to previous studies. [13]

In our study according to Status of immunoglobulin concentrations in active and inactive state of disease in JIA patients (n=33). Here according to Parameter, Active state of IgG (g/L), IgM (g/L) and IgA (g/L) were 13.04±4.41, 3.25±1.80 and 3.29±1.18 respectively. And Inactive state were of IgG (g/L), IgM (g/L) and IgA (g/L) were 9.88±2.31, 1.82±0.88 and 1.34±0.47 respectively.This result was similar with previous studies.[14] Another study found that there was elevation of IgG and IgA levels but IgM level was normal in active disease state with JIA patient.[15] Some study also found elevations in serum IgG and selective depressions in serum IgA levels in active disease states.[16]In this study the patients according to Diagnosis of JIA of 33 Patients, 22(66.7%) were Oligo and 11(33.3%) were Poly.Previous study had shown similar results.[17]Patients who may have more aggressive disease may also be identified by the IgA isotype's presence.[18]Changes of concentration of IgG, IgM and IgA in active and inactive state was statistically significant (p< 0.001). Study done by Torre et al shows immunoglobulin concentration became low to normal range in inactive state but IgA concentration were still high in large number of patients.[19]

We subdivided the total JIA patient into oligo articular and poly articular JIA group and measured concentration of immunoglobulin (IgG, IgM and IgA). These findings were comparable with previous studies.[20] In our present study. AbnormalIgG concentrations in active state was in 14 (42.5%) and in inactive state was in 1 (3%) JIA patient (P<0.001). Abnormal IgM concentrations in active state was in 20 (60.6%) and inactive state was in none patients (P<0.001). Abnormal IgA concentrations in active state was in 27 (81.8%) and in inactive state was in 2 (6.1%) patients (P<0.001).In the present study IgG, IgM, IgA concentration became normal in significant number of cases during inactive state of disease. Rackham OJ et al found similar result whwre IgG, IgM and IgA concentration significantly fall in inactive disease state.[21] It is expected that most of the patients have abnormal concentration ofimmunoglobulins at presentation during initial active diseases state which would become normal after treatment during inactive disease state. Treatment is being done by immunomodulator drug so, concentration of immunoglobulins can be altered. Determination of

serum immunoglobulin concentration is a potential importance in understanding pathogenetic processes involved in autoimmune and inflammatory disorders.[22]

Limitation of the Study

This was a small sample size prospective comparative hospital-based study. As a result, the findings of this study may not accurately reflect the situation in the entire country.

CONCLUSION

JIA is a chronic, debilitating childhood disorder with many long-term consequences. Diagnosis is based mainly on clinical symptoms, and accurate classification of JIA disease subtype is extremely important. The study concluded that high and abnormal levels of immunoglobulin (IgG, IgM, and IgA) is present among JIA patient in active disease state which became normal in inactive state.

RECOMMENDATION

This study can serve as a pilot to much larger research involving multiple centers that can provide a nationwide picture, validate regression models proposed in this study for future use and emphasize points to ensure better management and adherence.

ACKNOWLEDGEMENT

The wide range of disciplines involved in Comparison of Serum Immunoglobulin (IgG, IgM and IgA) Concentration During Active and Inactive Disease States in Patients with Juvenile Idiopathic Arthritis (JIA) research means that an editor's needs much assistance from referees in the evaluation of papers submitted for publication. I am very grateful to many colleagues for their thorough, helpful and usually prompt response to requests for their opinion and advice.

REFERENCES

1. Mahmud SA, Binstadt BA. Autoantibodies in the pathogenesis, diagnosis, and prognosis of juvenile idiopathic arthritis. Frontiers in immunology. 2019 Jan 14;9:3168.
2. Prakken B, Albani S, Martini A. Juvenile idiopathic arthritis. The Lancet. 2011 Jun 18;377(9783):2138-49.

3. Barden, J., Mullinax, F. and Waller, M., 1967. Immunoglobulin levels in rheumatoid arthritis: comparison with rheumatoid factor titers, clinical stage and disease duration. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*, *10*(3), pp.228-234.

4. Martini A, Lovell DJ. Juvenile idiopathic arthritis: state of the art and future perspectives. Annals of the Rheumatic Diseases. 2010 Jul 1;69(7):1260-3.
5. Ojiugo C I, Chidiebere I I, Constance N N. Evaluation of Serum Immunoglobulins and Body Mass Index in Young Adult Females with Striae Distensae in Imo State University, Owerri. Asian Journal of Research in Dermatological Science. 2022 Mar 23.

6. Wallace, C.A., Ruperto, N., Giannini, E., Childhood Arthritis and Rheumatology Research Alliance, Pediatric Rheumatology International Trials Organization and Pediatric Rheumatology Collaborative Study Group, 2004. Preliminary criteria for

clinical remission for select categories of juvenile idiopathic arthritis. *The Journal of rheumatology*, *31*(11), pp.2290-2294.

7. Aho, K., Heliövaara, M., Knekt, P., Reunanen, A., Aromaa, A., Leino, A., Kurki, P., Heikkilä, R. and Palosuo, T., 1997. Serum immunoglobulins and the risk of rheumatoid arthritis. *Annals of the rheumatic diseases*, *56*(6), pp.351-356.

8. Sitcharungsi, R., Bunupuradah, T., Pornvoranunt, A., Apornpong, T., Ananworanich, J., Khupulsup, K., Nouanthong, P., Vilaiyuk, S., Phasomsap, C., Kamchaisatian, W. and Pancharoen, C., 2013. Immunoglobulin values in healthy Thai children aged≤ 24 months determined by nephelometry. *Asian Pac J Allergy Immunol*, *31*(4), pp.307-313.

9. de la Torre, I., Leandro, M.J., Edwards, J.C. and Cambridge, G., 2012. Baseline serum immunoglobulin levels in patients with rheumatoid arthritis: relationships with clinical parameters and with B-cell dynamics following rituximab. *Clinical and Experimental Rheumatology-Incl Supplements*, *30*(4), p.554.

10. Cassidy, J.T., Petty, R.E., Laxer, R.M. and Lindsley, C.B., 2010. *Textbook of pediatric rheumatology E-Book*. Elsevier Health Sciences.

11. Ogilvie, E.M., Khan, A., Hubank, M., Kellam, P. and Woo, P., 2007. Specific gene expression profiles in systemic juvenile idiopathic arthritis. *Arthritis & Rheumatism*, *56*(6), pp.1954-1965.

12. Bukulmez, H. and Passo, M.H., 2002. Classification of juvenile chronic idiopathic arthropathies: Is it time to change yet?.*Bulletin on the Rheumatic Diseases*, *51*(5), p.1.

13. Williamson, A.A. and McColl, G.J., 2001. Early rheumatoid arthritis: can we predict its outcome? *Internal medicine journal*, *31*(3), pp.168-180.

14. Agarwal, S., Misra, R. and Aggarwal, A., 2008. Interleukin 17 levels are increased in juvenile idiopathic arthritis synovial fluid and induce synovial fibroblasts to produce proinflammatory cytokines and matrix metalloproteinases. *The Journal of rheumatology*, *35*(3), pp.515-519.

15. Ogilvie, E.M., Fife, M.S., Thompson, S.D., Twine, N., Tsoras, M., Moroldo, M., Fisher, S.A., Lewis, C.M., Prieur, A.M., Glass, D.N. and Woo, P., 2003. The− 174G allele of the interleukin- 6 gene confers susceptibility to systemic arthritis in children: a multicenter study using simplex and multiplex juvenile idiopathic arthritis families. *Arthritis & Rheumatism*, *48*(11), pp.3202-3206.

16. Liu, Y., Li, J.U.A.N., Chen, B.A.O.T.I.A.N., Helenius, H.A.N.S. and Granfors, K.A.I.S.A., 2001. Familial aggregation of ankylosing spondylitis in Southern China. *The Journal of Rheumatology*, *28*(3), pp.550-553.

17. Azam, S., Dipti, T. and Rahman, S., 2012. Prevalence and clinical pattern of juvenile idiopathic arthritis in a semi- urban area of B angladesh. *International Journal of Rheumatic Diseases*, *15*(1), pp.116-120.

18. Syed RH, Gilliam BE, Moore TL. Rheumatoid factors and anticyclic citrullinated peptide antibodies in pediatric rheumatology. Current rheumatology reports. 2008 Apr;10(2):156-63.

19. Hofer, M. and Southwood, T.R., 2002. Classification of childhood arthritis. *Best Practice & Research Clinical Rheumatology*, *16*(3), pp.379-396.

20. Gilliam, B.E., Chauhan, A.K., Low, J.M. and Moore, T.L., 2008. Measurement of biomarkers in juvenile idiopathic arthritis patients and their significant association with disease severity: a comparative study. *Clinical and experimental rheumatology*, *26*(3), pp.492-497.

21. Berntson, L., Gäre, B.A., Fasth, A., Herlin, T., Kristinsson, J., Lahdenne, P., Marhaug, G., Nielsen, S., Pelkonen, P., Rygg, M. and Nordic Study Group, 2003. Incidence of juvenile idiopathic arthritis in the Nordic countries. A population-based study with special reference to the validity of the ILAR and EULAR criteria. *The Journal of rheumatology*, *30*(10), pp.2275-2282.

22. Abraham, R.S., Barnidge, D.R. and Lanza, I.R., 2013. Assessment of proteins of the immune system. In *Clinical Immunology: Principles and Practice: Fourth Edition* (pp. 1145-1159). Elsevier Inc.