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Evaluation of inflammatory markers in Juvenile-onset Ankylosing Spondylitis (10-18years)

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Background

Juvenile-onset ankylosing spondylitis (JOAS) is a chronic inflammatory disease, which involves the spine, peripheral joints and entheses and affects children < 18 years. Therefore, the purpose of the present study was to compare the levels of inflammatory markers in juvenile onset Ankylosing Spondylitis (JOAS) patients.

Methods: JOAS patients were enrolled from the tertiary medical center from Sep 30th, 2019 to Nov. 30th, 2021. The demographic data, clinical symptoms/signs, Bath AS indices, HLA-B27, inflammatory markers, radiological findings, and treatment history were acquired with questionnaires, clinical evaluation, and chart review. The differences between serum levels of inflammatory markers in JOAS patients and healthy control were evaluated.

Results: A total of 88 patients (68 males, 20 females) were included, comprising 44 JOAS patients (mean age- 12.8 ± 2.7 years) and 44 healthy controls (mean age- 15.0 ± 2.4 years). Our patients (80.0% of JOAS and 50.0% of healthy controls volunteers) had physical trauma in the 1 month before disease onset. Also, 60.0% of JOAS patients had intense physical training. There was a trend of higher scores in Bath AS Disease Activity Index (BASDAI), and Bath AS Metrology Index (BASMI) score in JOAS patients as compare to healthy control volunteers ($p<0.05$). As to the laboratory and radiological tests, JOAS patients had higher levels of C-reactive protein and erythrocyte sedimentation rate.

Conclusion: JOAS presented more severe arthritis at disease onset and at any time of the course. If treated early and effectively, JOAS will not lead to a worse functional outcome

Introduction

Ankylosing Spondilitis is one of a family of chronic inflammatory disorders (spondyloarthropathies) primarily affecting peripheral and axial joints of the body. It is

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considered a "primary" disease because there seems to be no causal event producing it, whereas Reiter's syndrome, psoriatic arthritis, enteropathic (intestinal) arthritis, and others, are considered "reactive" because they seem to occur as a result of other inflammatory conditions (Chen CH et al 2007). As reported in a Harvard Health Letter Special Report, apparently Ankylosing Spondilitis has been with humans since the dawn of civilization (Textbook of Internal Medicine, 1989). In 1912, an Egyptologist unearthed a mummy from around 2,900 B.C. whose spine was as rigid as a block of stone from the sacrum to the neck. According to studies of Egyptian mummies, Ankylosing Spondilitis has been with mankind since at least 2,900 B.C. About 2,000,000 United States citizens suffer from a cluster of diseases that involve the spine and arthritis (Leon Chaitow ND et al 1989). Among these are about 300,000 who find themselves suffering from inflammation and gradual abnormal immobility and consolidation of a joint (ankylosis) primarily of the spine and adjacent spinal (paraspinal) structures. Leon Chaitow, N.D., D.O., the editor of the International Journal of Alternative and Complementary Medicine, United Kingdom osteopath and acupuncturist, found that, in the United Kingdom, about 80,000 were severely affected, while about 750,000 were less acutely affected. Chaitow's estimates probably mean that, in the United States, considerably more than 300,000 may be acutely affected, with millions of other people suffering from related or associated conditions.

Ankylosing spondylitis (AS) has been classically recognized as a disease of young adult males Garcia-Morteo O et al 1983) . However, although less frequently, it may also occur during childhood. It has been estimated that 15% of AS begins during the childhood years. In children, early symptoms may be easily confused with those of other rheumatic diseases, mainly juvenile rheumatoid arthritis (Aggarwal A et al 2005). The characteristics of the disease features of juvenile onset Ankylosing spondylitis(JOAS) and its comparison with those of the adult onset AS have been thoroughly studied (Lin YC et al 2009 & O'Shea FD et al 2009). In terms of advancing current knowledge about AS, JOAS has been regarded as a critical aspect of the disease for both prognostic and genetic studies. But an important unresolved issue has been whether JOAS, by virtue of a distinctive clinical course, is a clinical entity in its own right or just an earlier onset variant of AOAS. The present report describes the clinical findings in 44 patients with AS of juvenile onset (JOAS) and its comparison with healthy volunteers. Therefore the present research described the physicians to assess the early onset of JOAS via analysing the inflammatory markers.

Material and methods

The study was a prospective observational study on YOAS. In this study, correlation of inflammatory marker and YOAS was assessed to know the earlier onset of risk of AS in healthy volunteers. With this purpose, the study was conducted from Sep 30th, 2019 to Nov. 30th,2021 in Rajshree Medical Research Institute Bareilly, Uttar Pradesh India and approved by the local ethical review committee with a letter no RMRI/IEC/2020/0014 on dated 01/08/2019.

Population under study:-

88 participants were selected from Rajshree Medical Research Institute Bareilly, Uttar Pradesh India. Only those participants were included who fulfilled the criteria. Patients with ages between 10-18 years were assessed for Ankylosing Spondilitis by faculty members of

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the department of Orthopaedics, Medicine and Biochemistry, Rajshree Medical Research Institute Bareilly UP, India as per the guidelines mentioned in Fink CW et al 1995).

In the exclusive criteria, patients with a history of smoking, alcohol consumption, were excluded. The participants having inadequate responses to the classical treatment for AS were ineligible for the assessment of biochemical markers. The participants who were noticed with toxicity and adverse effect of the drugs were excluded from the study.

The study population of 88 patients was divided in two groups. Group A included forty four YOAS and Group B included forty four healthy volunteers. Group B participants were followed up for 6 months and are asked to visit the hospital after every 30th days up to six months. The vital parameters like blood pressure, pulse and any adverse reaction from the selected drugs were keenly observed by trained nurses. Biochemical markers related to the study were assessed at the time of enrolment of the patients and healthy volunteers. We addressed this issue by analysing a well-characterised cohort of patients with AS followed prospectively using a uniform protocol that incorporates clinical, laboratory and radiology data in a common database. We then divided this AS cohort into two subgroups depending on the age of onset of musculoskeletal symptoms (JOAS). These two groups of with and without AS were then compared

Questionnaire

During face-to-face interviews, each patient completed a comprehensive questionnaire that was composed of 5 main sections: (1) basic personal data; (2) factors possibly related to AS (Gastro intestinal or Gastro urinary infection, physical trauma history which made a patient visit a doctor, intense physical training, heavy work) in the 1 month antecedent to disease onset, and history of National cadet corps (NCC); (3) family history (relatives within the third degree) of AS and uveitis, psoriasis, inflammatory bowel disease (IBD); (4) disease course (age at disease onset, symptoms, diagnosis and treatment) and extra musculoskeletal manifestations (uveitis, immunoglobulin A [IgA] nephropathy, and colitis diagnosed by specialists); (5) Bath AS indices with a 0–10 cm visual analog scale (VAS), including the Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI), and Bath AS Patient Global Assessment (BAS-G) (Garrett S et al 1994, Jenkinson TR et al 1994 & Jones SD et al 1996).

Clinical evaluation

The medical chart of each patient was reviewed. A single rheumatologist performed a thorough physical examination for each subject, including any synovitis or enthesitis, range of motion (ROM) of the spine and peripheral joints, and chest expansion. The value measured was then transformed into each item for the Bath AS Metrology Index (BASMI)(Wewers ME et al 2010).

Laboratory tests (Merck manual , 16th edition , 1992)

The erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), and serum IgA are 3 markers that are usually used to evaluate the disease activity of AS. ESR was measured with the Westergren method. Serum CRP and IgA levels were measured by nephelometry. The 3 indices were measured on the day of the interview (present value). We also retrospectively collected the values of the 3 indices recorded in the medical chart on the 1st day of visit to our

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hospital for AS (initial value) and the highest values during the entire clinical course (peak value). In addition, HLA- B27 typing was done by flow cytometry.

Statistical analysis

The Kolmogorov-Smirnov goodness-of-fit test and normal probability plot were measured for the distributional characteristics of the clinical parameters (BASDAI, BASFI, BAS-G) and the physical parameters. For parameters had indicated that the normally distributed quite robust and the use of parametric statistical techniques seemed to be appropriate, absolute differences and 95% confidence intervals (CI) between patients with and without AS were used to analyse group differences. Otherwise, the Mann–Whitney U test was used as a non-parametric method to analyse group differences. A p value <0.05 was considered significant.

Table 1- Demographic and clinical parameters of YOAS patients and healthy control volunteers

	Characteristics	**YOAS patients (n=44)**	**Healthy control volunteers (n=44)**	***P* value**
1	**Age**	12.8±4.6	11.5±5.1	0.106
2	**Male/ Female**	30/14	32/12	0.771
3	**Peripheral joint involvement**	28(63.6)	04(10.0)	0.114
4	**HLA-B 27(+)**	39(88.6)	Nil	
5	**BASDAI**	4.98(2.44)	1.14(0.98)	0.108
6	**BASFI**	2.91(2.51)	018(0.27)	0.933
7	**BAS-G**	5.81(2.27)	0.94(0.88)	0.860
8	**BASMI**	1.98±2.18	0.11±0.07	0.298
9	**Occiput to wall**	4.27 (8.04)	0.17(0.34)	0.461
10	**Chest expansion**	3.14(2.02)	0.24(0.27)	0.515
11	**ESR mm/hr**	48.4±26.8	8.1±6.4	0.032
12	**CRP mg/dL**	2.47±2.68	0.18±0.11	0.031
13	**IgA mg/dL**	585.1±381.6	90.8±21.4	0.12
14	**Serum soluble cytokine receptor pg/mL**	509.8±389.7	1.38±0.42	
15	**Sacroiliac joint**			0.266*
	Grade 0	0(0)	0(0)	
	Grade 1	0(0)	0(0)	
	Grade 2	18(40.9)	0(0)	
	Grade 3	05(11.3)	0(0)	
	Grade 4	19(43.1)	0(0)	

Note –

HLA (Human leukocyte antigen, BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), BASFI (Bath Ankylosing Spondylitis Function Index), BAS-G (Bath Ankylosing Spondylitis Global Score), BASMI (Bath Ankylosing Spondylitis Metrology Index).

Data presented as n(%) for categorical variables and mean SD for continuous variables, p values are determined by Mann- Whitney U test as a nonparametric method, statistical significant if p <0.05, * comparisons performed with chi test for categorical variables.

Results

Demographics

Table 1 shows the demographics and clinical characteristics of the 44 YOAS patients with 44 healthy volunteers. In this tertiary care hospital in Bareilly, Uttar Pradesh, India, 30 (68.1%) of 44 those with YOAS. The population under study was divided into two subgroups: with or

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without a history of YOAS. Clinical parameters were compared between subgroups (Table 1). There was no statistically significant difference between YOAS patients with and without AS in age (p=0.106), and male-to-female ratio (p=0.771). Patients with YOAS had no significantly higher peripheral joint involvement rate than those without (p=0.114).

Eighty eight precent (39/44) of patients with YOAS had positive HLA-B27. Disease activity, functional ability and patient's global assessment with the history of YOAS seem to have an influence on disease activity (BASDAI) in YOAS patients (Table 1). Patients with YOAS had significantly higher BASDAI values than those without [Mean (SD) 4.98(2.44)vs. 1.14(0.98). On the other hand, the occurrence of YOAS showed a significant effect on functional ability (BASFI) in our study. Patients with YOAS had significantly higher BASFI values than those without [mean (SD), 2.91(2.51)vs. 018(0.27). In addition, the BAS-G value was higher in patients with YOAS than in those without, but the difference was statistically significant [mean (SD), 5.81(2.27)vs. 0.94(0.88).

Physical examinations

Among the physical findings, it is of interest that occiput-to-wall distances were significantly increased in patients with YOAS than those without (p=0.461). Chest expansion also showed reduced length in patients with YOAS compared with those without although no significant differences were reached(p= 0.515). Based on the above results, AS patients with a history of YOAS had a relatively severe physical limitation than those without.

Soluble cytokine receptor levels The mean serum soluble cytokine receptor levels were 509.8±389.7pg/ml as compared to healthy controls where the levels were 1.38±0.42 pg/ml. There was a significant positive correlation of serum soluble cytokine receptor levels with CRP ($R = 0.33$, $p < 0.001$) and ESR ($R = 0.30$, $p = 0.01$). There was no correlation of serum soluble cytokine receptor levels with BAS- DAI.

Discussion

The occurrence rate of AAU may be various among different regions and populations due to the different genetic backgrounds. The prevalence of AAU in AS patients in this Chinese hospital cohort was 15.8%, which was quite similar to the previous Chinese cohort in Singapore (17%) (Hong C et al 2019 and Chen Ch et al 2007). In contrast, our study showed a higher prevalence of YOAS in AS patients have been reported, ranging from 30∼50%.

Among 44 YOAS patients, 30 YOAS patients (88.1%)in our study were positive for HLA-B27 while 14/44 of YOAS patients with YOAS were HLA-B27 negative, suggesting that patients with YOAS have a trend to a higher positive HLA-B27 rate (Chen B et al 2017). A similar report by Jaakkola et al. showed that HLA-B27-positive rates were significantly higher in AS patients with AAU than those without [98% (123/126) vs. 88% (122/138)]. Similar results from another group also showed that higher prevalence of AAU occurred in HLA-B27(+) AS patients than those HLA-B27(−).

In our study, a significantly higher BASDAI value was found in YOAS patients as compared with those without YOAS. Patients with a history of YOAS seemed to have higher disease activity. A previous study demonstrated that the incidence of YOAS in AS patients decreased after treatment with anti-tumor necrosis factor agents (Zochling J et al 2011). By taking the results from our and other studies, the relationship between disease activity and YOAS is correlated. Our results also showed that AS patients with YOAS had a significantly higher

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BASFI score than those without. In addition, a higher BAS-G was observed in those patients with YOAS, but it did not reach significance compared with those without YOAS. Our results showed that YOAS patients had higher disease activity (BASDAI), poorer functional ability (BASFI) and advanced physical limitation. YOAS has one of the most common extra-articualr manifestations. Overall, the development of YOAS in AS patients may appear to have a poor functional outcomes. Studies are needed to elucidate the association between the occurrence of YOAS and functional outcome.

The AS patients with YOAS suffered from advanced physical restriction compared with those without. Distance of occiput-to-wall significantly increased in patients with YOAS. In addition, the length of chest expansion was decreased, but no statistical significance was reached. Koo BS et al. 2016 showed that the group of AS patients with radiological abnormalities of the cervical spine has a significantly higher prevalence of AAU than those without such radiological features (68% vs. 25%, $p<0.01$), demonstrating that AS patients with AAU has advanced skeletal damage. Taken together, the presence of YOAS in AS patients may be associated with a further severe physical limitations. We did find a significant positive correlation of Serum soluble cytokine receptors with the inflammatory markers ESR and CRP. There is no correlation of serum cytokine receptors with BASDAI(Tsui et al 2010).

Conclusion

In conclusion, AS patients with a history of YOAS are at higher risk of developing severe disease activity, poor functional ability and advanced physical impairment. However, this conclusion cannot be established on a cross-sectional study only. To study the association between the occurrence of YOAS and AS disease outcome, long-term records of the change in disease activity and functional status is necessary.

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