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Seroprevalence of *Helicobacter pylori* in Juvenile Rheumatoid Arthritis And its Relation to Disease Severity

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We aimed to evaluate seroprevalence of *Helicobacter pylori* (*H. pylori*) IgG antibodies in children with Juvenile rheumatoid arthritis (JRA) and to assess the effect of its eradication treatment on various symptoms and inflammatory indices, to find out whether there is a possible link between this bacterium and disease severity. This study included 21 children with JRA (10 males and 11 females) with a mean age (10.5±4.5 years). Eighteen healthy children matched in age and sex were used as a control group. All subjects had undergone full clinical examination and laboratory investigations including complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor, anti-nuclear antibodies, serum albumin, α1-globulin, α2-globulin, β-globulin and γ-globulin. *H. pylori* IgG antibodies detection was done by ELISA technique. We found that 61.9% of patients with JRA were seropositive for *H. pylori* IgG, whereas only 27.8% of the healthy children were seropositive ($p<0.05$). Red cell indices and albumin were statistically significantly higher in healthy children than JRA patients ($p<0.05$). ESR was statistically significantly higher in JRA patients than controls ($p<0.05$). The number of swollen joints correlated positively with β-globulin, ESR and CRP ($r = 0.43$, $p = 0.048$; $r = 0.67$, $p = 0.001$ and $r = 0.54$, $p = 0.01$, respectively). Comparison between *H. pylori* seropositive and seronegative JRA patients revealed that ESR and CRP were statistically significantly higher in *H. pylori* seropositive JRA patients than seronegative patients ($p<0.05$). Gastrointestinal symptoms were significantly more obvious in the former subgroup ($p<0.05$). Hemoglobin level, hematocrite and serum albumin were statistically significantly lower in *H. pylori* seropositive than seronegative JRA patients ($p<0.05$), while α1-globulin, α2-globulin, β-globulin and γ-globulin showed no significant differences between both subgroups ($p>0.05$). Six months after starting *H. pylori* eradication treatment; the clinical parameters of JRA and ESR were statistically significantly lower in *H. pylori* seropositive JRA patients than the base line values ($p<0.05$). They showed progressive improvement of all clinical parameters over time. In conclusion: *H. pylori* seroprevalence is more frequent in JRA patients than healthy children. It might have a role in the pathogenesis of JRA and might be implicated in aggravating severity of symptoms since treatment for its eradication might induce progressive and considerable improvement of both clinical symptoms and laboratory investigations.

Key words: Juvenile rheumatoid arthritis, *Helicobacter pylori*, prevalence, eradication treatment

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INTRODUCTION

Rheumatoid Arthritis (RA) is an autoimmune disease that can cause irreversible joint deformities and functional impairment. It results from an autoimmune reaction to unknown stimuli or infection with as yet unidentified micro-organisms; however other factors may be contributing (Choy and Panayi, 2001; Silman and Pearson, 2002; Berglin *et al*., 2004).

An infectious aetiology of RA has also been postulated, but although many germs have been proposed as the triggering agent, none has been identified. Several antibiotics have also been shown to be effective for patients with mild to moderate RA, although their mechanism of action remains unclear (McConkey and Situnayake, 1988; Tilley *et al*., 1995; O'Dell, 1999).

The role of *Helicobacter pylori* infection is explored in more and more extragastric diseases including rheumatic disorders (Carloni *et al*., 2000; Konturek and Hahn, 2001; Zentilin *et al*., 2002; Gasbarrini *et al*., 2003).

It is a common bacterial infection among humans throughout the world, with a higher prevalence in developing than in developed countries. Current knowledge implies that acquisition of *H. pylori* seems to occur predominantly in childhood and a major role of intrafamilial spread is now beyond controversy; so it seems logical to diagnose and treat this infection in childhood (Kolacek, 2002; Versalovic, 2003 and Kim, 2005).

Proposed mechanisms underlying extragastric pathogenicity associated with *H. pylori* include a direct effect of the bacterium: Activation of inflammatory processes, with a release of cytokines and flogistic mediators with subsequent systemic effects responsible for the remote manifestations of the disease and finally mimicry between bacterial and host antigens (Gasbarrini *et al*., 2003). So, it is said that, *H. pylori* induces the host's constitutional immune response against various antigens of this bacterium. The detection of immunoglobulin G (IgG) antibodies to *H. pylori* (*H. pylori* IgG) is useful for the diagnosis of infection. Some investigators reported that the titers of these antibodies declined during therapy for *H. pylori* eradication (Cutler and Prasad, 1996; Perez *et al*., 1997).

It was reported that a consistent decrease in the IgG antibody titer within 6 months of antimicrobial therapy reliably indicated the eradication of *H. pylori* (Kosunen, 1995). Accordingly, serologic testing represents a primary screening approach for evaluation of *H. pylori* status in patients (McColl *et al*., 2002; Versalovic, 2003).

So far, the potential role of *H. pylori* infection in juvenile rheumatoid arthritis (JRA) has been poorly investigated and there have been conflicting data about it.

The aim of this study was to evaluate seroprevalence of *H. pylori* IgG antibodies in children with JRA and to assess the effect of its eradication treatment on various symptoms and inflammatory indices, in order to find out whether there is a possible link between this bacterium and disease severity.

MATERIALS AND METHODS

This study was conducted on 21 children suffering from JRA (10 males and 11 females), with a mean age (10.5±4.5 years) and age ranged from 3.5-18 years. They were recruited from the outpatient clinic of Collagen, New Children's Hospital, Cairo University as well as from the Pediatrics Clinic of the National Research Center. Each patient satisfied the 1987 American College of Rheumatology (ACR) criteria for RA (Arnett *et al*., 1988). Eighteen healthy age and sex matched children (12 males and 6 females), with a mean age (9.03±3.99 years) were included as a control group. They had no history of arthritis, dyspeptic symptoms or abdominal pain.

Exclusion criteria included those who received eradication treatment for *H. pylori* or other antibiotics and those with fever or infectious diseases. Parental consent was taken from all participants of the study.

All groups were subjected to full medical history taking and thorough clinical examination including weight and height with careful examination of joints.

The clinical activity of the disease was assessed by both the investigator and the patients or their parents. In each patient the joints with active arthritis at the time of the study were counted. Active disease was defined by the presence of at least 3 of the following criteria:

- Three or more swollen joints.
- Six or more tender or painful joints on motion.
- Morning stiffness >45 min in duration.
- ESR >40 mm first h.

Patients with JRA who were *H. pylori*-IgG seropositive were given treatment for its eradication in the form of amoxicillin and metronidazole. They were evaluated at the beginning (baseline) and at the end of the study, where clinical and laboratory findings of disease activity were followed up for 6 months.

Laboratory investigations: Before initiation of eradication treatment, 5 mL of venous blood samples were withdrawn

from all subjects and were divided into 2 tubes. Two milliliter of the sample were added to EDTA and 3 mL were put in plane tubes (without anticoagulant) and centrifuged then the separated sera were kept frozen at -20°C until analysis. Another blood sample was withdrawn from *H. pylori* seropositive JRA patients at the end of the study.

The following laboratory investigations were done: Complete Blood Count (CBC), Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), Rheumatoid Factor (RF), Anti-Nuclear Antibodies (ANA), Albumin, α1-globulin, α2-globulin, β-globulin and γ-globulin as well as *H. pylori* IgG antibodies measurement.

- *Helicobacter pylori*-IgG antibodies detection was done by enzyme linked immunosorbent assay using Biotest Anti-*Helicobacter pylori* IgG ELISA Kit, Art. No.807780, Biotest AG, Landsteinerstrasse 5, D-63303 Dreieich, Germany (Hess, 1997).
- Albumin, α1-globulin, α2-globulin, β-globulin and γ-globulin components of serum total protein were measured by protein electrophoresis using cellulose acetate paper. Detection of them was done by Helna (Junior-France S.A.).

Statistical methods: Statistical Package for Social Sciences (SPSS) version 11 was used for analysis of data. Data were summarized as mean±SD and percentage. Student's t-test for quantitative independent variables was used for analysis of difference between two groups and Chi square test was used for qualitative variables. Correlations between various variables were done using Pearson correlation coefficient (r). p-value was considered significant if less than 0.05.

RESULTS

All JRA children had polyarticular onset JRA, 9 of them were RF positive. Duration of disease ranged from 1-14 years with a mean of (4.00±3.05 years). All children with JRA (100%) were receiving non-steroidal anti-inflammatory drugs (NSAID), 17 (81%) were being treated with methotrexate and 17 (81%) with antimalarial drugs. Corticosteroids had been given to 7 (33.3%) patients and gastroprotective drugs were given to 20 (95.2%) patients.

Table 1 demonstrates comparison of the clinical and laboratory data between patients with JRA and healthy children of the control group. Red cell indices and serum albumin were higher in the control group than in JRA patients and the difference was statistically significant ($p<0.05$). On the other hand, ESR was statistically significantly higher in JRA patients than the control group ($p = 0.0001$).

Table 1: Comparison of demographic and laboratory findings in juvenile rheumatoid arthritis patients and healthy children

Items	§JRA patients (n = 21)	Healthy children (n = 18)	p-value
Male: female (N. and %)	10 (47.6): 11 (52.4)	12 (60) : 6 (30)	0.33
Age (years)	10.5± 4.5	9.03±3.99	0.28
Weight (kg)	28.47±14.23	35.77±12.55	0.1
Height (cm)	127.40±25.19	133.77±20.47	0.39
RBCs ($\times 10^6$ mm^{-3})	4.1±1.03	4.67±0.44	0.037*
Hemoglobin (g dL^{-1})	9.62±1.20	13.16±1.27	0.0001*
HCT (%)	30.81±3.41	39.36±4.7	0.0001*
MCV (fl)	75.52±6.76	84.15±4.44	0.0001*
MCH (pg)	23.60±2.7	27.88±1.42	0.0001*
MCHC (g dL^{-1})	31.05±1.83	32.8±1.5	0.003*
Total Leucocytic count ($\times 10^3$ mm^{-3})	7.27±2.7	6.17±1.16	0.13
ESR (mm h^{-1})	47.33±35.42	5.27±0.83	0.0001*
Albumin (g dL^{-1})	3.39±0.58	3.95±0.43	0.002*
H. pylori IgG seroprevalence (N. and %)	13 (61.9%)	5 (27.8%)	0.033*

Data were expressed as Mean±SD, except for numbers between parentheses
*p-value is significant if <0.05, §Juvenile rheumatoid arthritis

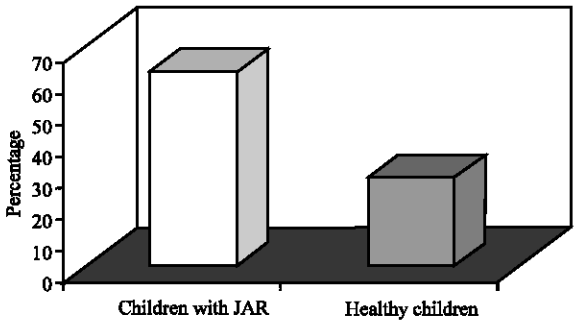

Fig. 1: Seroprevalence of *H. pylori* in patients with juvenile rheumatoid arthritis and healthy children

Figure 1 illustrates the seroprevalence of *H. pylori*-IgG. Out of the 21 JRA patients; 13 (61.9%) were *H. pylori* IgG seropositive while only 5 (27.8%) of the healthy children were seropositive ($p = 0.033$).

Regarding gastrointestinal symptoms; 12 (57.1%) of JRA patients complained of abdominal pain while none of the healthy children had abdominal pain ($p<0.05$).

The number of swollen joints correlated positively with β-globulin, ESR and CRP ($r = 0.43$, $p = 0.048$; $r = 0.67$, $p = 0.001$ and $r = 0.54$, $p = 0.01$, respectively).

Comparison of clinical and laboratory data between *H. pylori* IgG seropositive and seronegative JRA patients are summarized in Table (2-4).

There were no significant differences as regards age, weight, height, sex or duration of JRA between the 2 subgroups. Also, although the values of the number of painful/tender and swollen joints and the duration of morning stiffness were greater in *H. pylori* seropositive than seronegative JRA patients; yet the difference was

Table 2: Clinical characteristics of *H. pylori* seropositive versus seronegative juvenile rheumatoid arthritis patients at baseline

Items	*H. pylori* seropositive §JRA patients (n = 13)	*H. pylori* seronegative §JRA patients (n = 8)	p-value
Male: female (N. and %)	6 (46.2%): 7 (53.8%)	4 (50%): 4 (50%)	0.86
Age (years)	11.92±3.97	8.28±4.72	0.07
Weight (kg)	32.15±13.84	22.50±13.59	0.14
Height (cm)	134.31±23.29	116.19±25.53	0.11
Duration of JRA (years)	4.54±3.75	3.13±1.03	0.3
No. of painful/ tender joints	12.0±9.0	11.75±8.79	0.95
No. of swollen joints	4.31±2.63	2.88±1.55	0.18
Morning stiffness duration (min)	55.39±28.68	42.50±23.90	0.3
Gastrointestinal symptoms (N. and %)	10 (77%)	2 (25%)	0.02*

Data were expressed as Mean±SD, except for numbers between parentheses *p-value is significant if < 0.05, §Juvenile rheumatoid arthritis

Table 3: Comparison of C-reactive protein, rheumatoid factor and antinuclear antibodies in *H. pylori* seropositive versus seronegative juvenile rheumatoid arthritis patients

	˙CRP		‡RF		˙ANA	
Items	+ve	-ve	+ve	-ve	+ve	-ve
H. pylori seropositive §JRA patients (n = 13)	11	2	5	8	3	10
H. pylori seronegative §JRA patients (n = 8)	3	5	4	4	2	6
p-value	0.026*		>0.05		>0.05	

*p-value is significant if <0.05, ˙C-reactive protein, ‡Rheumatoid factor, ˙Antinuclear antibodies, §Juvenile rheumatoid arthritis

Table 4: Laboratory data of *H. pylori* seropositive versus seronegative juvenile rheumatoid arthritis patients

Item	*H. pylori* seropositive §JRA patients (n = 13)	*H. pylori* seronegative §JRA patients (n = 8)	p-value
HB (g dL^{-1})	8.98±0.91	10.70±0.76	0.0001*
HCT (%)	29.00±2.83	33.78±1.84	0.0001*
MCV (fl)	74.28±7.30	77.54±5.65	0.29
MCH (pg)	22.99±2.75	24.60±2.44	0.19
MCHC (g dL^{-1})	30.60±1.53	31.73±2.13	0.18
Total leucocytic count ($\times 10^3$ mm^{-3})	7.61±3.25	6.81±1.79	0.53
ESR (mm h^{-1})	64.92±34.16	18.75±8.70	0.001*
Albumin (g dL^{-1})	3.18±0.52	3.74±0.53	0.027*
α 1-globulin (g dL^{-1})	0.30±0.14	0.31±0.14	0.84
α 2-globulin (g dL^{-1})	0.69±0.17	0.70±0.11	0.91
β-globulin (g dL^{-1})	0.85±0.15	0.81±0.13	0.59
γ-globulin (g dL^{-1})	1.26±0.37	1.16±0.37	0.56

Data were expressed as Mean±SD, *p-value is significant if <0.05, §Juvenile rheumatoid arthritis

not significant (p>0.05). Only gastrointestinal symptoms were statistically more obvious in *H. pylori* seropositive than seronegative JRA patients (p = 0.02) (Table 2).

There was no significant difference between the two subgroups of JRA patients concerning RF and ANA (p>0.05). In contrast, CRP and ESR showed a statistically significant difference between both subgroups (p = 0.026 and p = 0.001, respectively) (Table 3 and 4).

Table 5: Clinical and laboratory data at baseline and after 6 months in treated *H. pylori* seropositive juvenile rheumatoid arthritis patients

Items	*H. pylori* seropositive JRA patients at baseline (n = 13)	*H. pylori* seropositive JRA patients after 6 months (n = 13)	p-value
No. of painful/ tender joints	12.0±9.0	6.46± 2.25	0.042*
No. of swollen joints	4.31±2.63	2.62± 1.33	0.049*
Morning stiffness duration (minutes)	55.39±28.68	23.85±11.39	0.001*
ESR (mm h^{-1})	64.92±34.15	15.92±11.75	0.0001*
HB (g dL^{-1})	8.96±0.90	10.68±1.98	0.009*

Data were expressed as Mean±SD, *p-value is significant if <0.05, §Juvenile Rheumatoid arthritis

Hemoglobin (Hb), Hematocrite (HCT) and serum albumin level were statistically significantly lower in *H. pylori* seropositive than seronegative JRA patients (p = 0.0001, p = 0.0001 and p = 0.027, respectively). On the other hand, although α1-globulin, α2-globulin, β-globulin and γ-globulin were greater than normal levels in both subgroups; yet they showed no significant differences between them (p>0.05) (Table 4).

As regards the effects of treatment for eradication of *H. pylori* in *H. pylori* IgG seropositive JRA patients; we found that the number of painful/tender and swollen joints, duration of morning stiffness and ESR were statistically significantly lower in those patients 6 months after treatment than the base line values (p = 0.042, p = 0.049, p = 0.001 and p = 0.0001, respectively). Moreover, Hb value was higher after the 6 months (p = 0.009) (Table 5).

DISCUSSION

H. pylori infection has been associated not only with chronic gastritis and peptic ulcer, but also with many extragastric disorders (Carloni *et al*., 2000; Konturek and Hahn, 2001; Zentlin *et al*., 2002; Gasbarrini *et al*., 2003). Among the latter, *H. pylori* has been implicated in the pathogenesis of several autoimmune-inflammatory diseases including, Sjogren's syndrome, systemic vasculitides, Henoch-Schönlein purpura, adult rheumatoid arthritis and others (Figura *et al*., 1994; Showji *et al*., 1996; Gasbarrini and Franceschi, 1999; Zentlin *et al*., 2002; Novak *et al*., 2003). Moreover, a high prevalence of Cag A-positive strains, the most virulent form of this bacterium, has been found in patients with other autoimmune diseases such as, systemic sclerosis (Danese *et al*., 2000).

There have been conflicting published data on the possible interactive role of *H. pylori* in the development of symptoms in RA (Grigoriadou *et al*., 2002).

Our study shows that the seroprevalence of *H. pylori* IgG antibodies in patients with JRA were

significantly higher than healthy children of the control group. It was also higher than the reported prevalence for healthy children in several studies (AL-Shamahy, 2005; Koch *et al*., 2005; Mukherjee *et al*., 2005; Parente *et al*., 2006). Still, it appears to be lower compared with the prevalence in other studies (Rodrigues *et al*., 2004, 2005).

Elezoglou *et al*. (2000) showed that patients with RA had a significantly higher H. pylori seropositivity than volunteers. Therefore this autoimmune disease is characterized by a high association with this familiar infection. On the other hand, other investigators reported that the prevalence of *H. pylori* was not greater in adult RA patients than normal subjects of the same age in Western countries (Grigoriadou *et al*., 2002; Zentlin *et al*., 2002).

The prevalence of *H. pylori* infection continues to vary markedly between developing and developed countries and ranges from 3.3% to 75.4% (AL-Shamahy, 2005; Garg *et al*., 2005; Iwanczak *et al*., 2005; Kim, 2005; Koch *et al*., 2005; Leandro *et al*., 2005; Mukherjee *et al*., 2005; Rodrigues *et al*., 2004 and 2005; Singh *et al*., 2006).

There was no sex difference in *H. pylori* seroprevalence in this study, which was in agreement with Huang *et al*. (2004), Kikuchi *et al*. (2005) and Mukherjee *et al*. (2005) who reported that the prevalence did not depend on sex. In contrast, Leandro *et al*. (2005) stated that the prevalence was significantly higher in boys. Also, a previous study of Replogle *et al*. (1995) in young adults showed a higher prevalence of infection in males.

The number of swollen joints in patients with JRA in our study correlated positively with β-globulin, ESR and CRP which were reported by Harris (1990) as indicators of disease activity.

The present results revealed that red cell indices were statistically significantly higher in the healthy children of the control group than patients with JRA which might be attributed to the chronicity of the disease that lead to anemia of chronic diseases. Also, the Hb level and HCT value were statistically significantly lower in *H. pylori* seropositive than seronegative JRA patients, which was concordant with Zentlin *et al*. (2002). Many investigators reported that *H. pylori* infection in children was associated with iron deficiency anemia (Ashorn *et al*., 2001; Kostaki *et al*., 2003; Cardenas *et al*., 2006).

Serum albumin level was statistically significantly lower in JRA patients than the control group and in *H. pylori* seropositive compared to seronegative JRA patients, which indicates gastrointestinal protein loss. Picco *et al*. (2000) reported that all of the subtypes of juvenile chronic arthritis that they studied displayed an increased intestinal permeability. Hence, gut wall inflammation (albeit asymptomatic) may also be present.

The fractions of electrophoresis: α1-globulin, α2-globulin, β-globulin and γ-globulin were more elevated in JRA patients than the normal levels; but there were no significant differences between both JRA subgroups. It was reported that they are indicators of disease activity with γ-globulin more indicative of chronicity (Zentilin *et al*., 2002).

Concerning gastrointestinal symptoms; our patients with JRA experienced abdominal pain, which was more obvious in *H. pylori* seropositive than seronegative JRA patients. This was in agreement with Ashorn *et al*. (2003) and Weber *et al*. (2003).

Although, our group of JRA patients with *H. pylori* seropositivity presented with a tendency for more severe clinical manifestations of the disease than seronegative JRA patients, mainly with regard to the number of painful/tender and swollen joints and duration of morning stiffness; still the difference between both subgroups was non significant. Additionally, the laboratory markers of activity tended to be elevated in the former subgroup than the later one, with significant differences only for ESR and CRP. These results seem to be a sign of a more marked inflammatory state in *H. pylori* IgG seropositive JRA patients and are consistent with Zentilin *et al*. (2002).

In contrast, Rybar *et al*. (2004) has not confirmed any differences between groups of *H. pylori* seropositive and seronegative RA patients. Also, a previous study in adult RA revealed that the severity of RA do not seem to depend upon *H. pylori* infection in RA patients (Ishikawa *et al*., 2002).

After 6 months of follow up in the current study, the anti-*H. pylori* treatment for its eradication prescribed to our *H. pylori* IgG seropositive JRA subgroup was successful. It was associated with gradual improvement of clinical symptoms compared with baseline. Also, laboratory indices of inflammation demonstrated a gradual and considerable reduction in *H. pylori*-treated JRA patients. This is an appropriate evidence of the significant decrease of inflammatory activity after treatment for *H. pylori* eradication. This was in accordance with Zentilin *et al*. (1999, 2000 and 2002) in their extended studies, who also added that the results were significantly better than in *H. pylori*-negative adult RA patients, whose parameters remained substantially unchanged during the same prolonged follow-up period. They reported that it remains a possibility that the medications intended to eradicate *H. pylori* may have had a therapeutic effect on arthropathy in the patients.

The exceeding findings appear to suggest a pathogenetic role of *H. pylori* in JRA. It is associated with

a higher disease activity, which decreases gradually and considerably after eradication treatment. It may contribute to conserve an inflammatory condition in response to the continuous antigenic stimulus induced by chronic infection. The immunological and inflammatory response by the host against the bacterium is determined by the direct or indirect production of various cytokines (Harris, 1990; Gasbarrini *et al*., 2003). It is possible that these factors act not only at a local level, but also in extradigestive areas, thus increasing the expression of inflammatory status in JRA. An alternative pathogenetic hypothesis could be the production of autoantibodies induced by the bacterium through a cross-reaction mechanism, which can act against gastric epithelial cells and other host tissues (Negrini *et al*., 1991, 1996).

We still wonder whether the association between *H. pylori* and JRA is causal or it is just an epiphenomenon. Many authors thought that, *H. pylori* can be involved in the aggravation of RA and in sustaining of the acute clinical symptoms for a prolonged period. *H. pylori*, however, is not a primary inducer of this disease. It is possible that the secondary immunodeficiency caused by the immunosuppressive therapy of JRA can lead to an increased susceptibility to H. pylori infection and the concomitant *H. pylori* infection can activate JRA. These speculations might be supported by the results of our current study which indicate the production of *H. pylori* IgG antibodies in the majority of JRA patients and a high percentage of them who have been on immunosuppressive therapy were *H. pylori* IgG seropositive.

CONCLUSIONS

Our findings show that, *H. pylori*-IgG seroprevalence is more frequent in JRA patients than healthy children. It seems to be associated with disease activity and gastrointestinal symptoms in them.

Anti *H. pylori* treatment carried out in our *H. pylori* IgG seropositive JRA subgroup appears to be useful as it was associated with progressive and considerable improvement of both clinical symptoms and laboratory investigations after treatment.

Accordingly, *H. pylori* might have a pathogenetic role of the disease as it may contribute to maintain inflammation in response to the constant antigenic stimulation induced by persistent infection.

RECOMMENDATIONS

It is suggested to serologically screen patients with JRA for *H. pylori* IgG antibodies which act as a highly accurate, simple and noninvasive test and it is recommended to give seropositive patients anti-*H. pylori* treatment for its eradication.

Further studies and investigations are required on a larger sample size of patients and for a longer time.

REFERENCES

Al-Shamahy, H.A., 2005. Seroprevalence of *H. pylori* among children in Sana'a, Yemen. Ann. Saudi. Med., 25: 299-303.

Arnett, F.C., S.M. Edworthy, D.A. Bloch, D.J. McShane, J.F. Fries, N.S. Cooper *et al*., 1988. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum, 31: 315-324.

Ashorn, M., T. Ruuska and A. Makipernaa, 2001. *Helicobacter pylori* and iron deficiency anaemia in children. Scand. J. Gastroenterol., 36: 701-705.

Ashorn, M., P. Verronen, T. Ruuska and H. Huhtala, 2003. Upper endoscopic findings in children with active juvenile rheumatoid arthritis. Acta Paediatr, 92: 558-561.

Berglin, E., L. Padyukov, Sundin Ulf, G. Hallmans, H. Stenlund, van W.J. Venrooij, L. Klareskog and S.R. Dahlqvist, 2004. A combination of autoantibodies to Cyclic Citrullinated Peptide (CCP) and HLA-DRB1 locus antigens is strongly associated with future onset of rheumatoid arthritis. Arthritis Res. Ther., 6: 303-308.

Cardenas, V.M., Z.D. Mulla, M. Ortiz and D.Y. Graham, 2006. Iron deficiency and *Helicobacter pylori* Infection in the United States. Am. J. Epidemiol., 15: 127-134.

Carloni, E., F. Cremonini, S. Di Caro, C. Padalino, L. Gerardino, A. Santoliquido, S. Colasanti, P. Pola and A. Gasbarrini, 2000. *Helicobacter pylori*-related extradigestive diseases and effects of eradication therapy. Dig. Liver Dis., 32: S214-S216.

Choy, E.H.S. and G.S. Panayi, 2001. Mechanisms of Disease: Cytokine pathways and joint inflammation in Rheumatoid arthritis. N. Eng. J. Med., 344: 907-916.

Cutler, A.F. and V.M. Prasad, 1996. Long-term follow-up of *Helicobacter pylori* serology after successful eradication. Am. J. Gastroenterol., 91: 85-88.

Danese, S., A. Zoli, F. Cremonini and A. Gasbarrini, 2000. High prevalence of *Helicobacter pylori* type I virulent strains in patients with systemic sclerosis. J. Rheumatol., 27: 1568-1569.

Elezoglou, A.V., G.J. Mantzaris and S.V. Delakidis *et al*., 2000. Incidence of *Helicobacter pylori* infrection in patients with rheumatic diseases. Gut, 47 (Suppl. 1) (Abstract).

Figura, N., N. Giordano, D. Burroni *et al*., 1994. Sjögren syndrome and *Helicobacter pylori* infection. Eur. J. Gastroenterol. Hepatol., 6: 321-322.

Garg, P.K., S. Perry, L. Sanchez and J. Parsonnet, 2005. Concordance of *Helicobacter pylori* infection among children in extended-family homes. Epidemiol. Infect., 11: 1-10.

Gasbarrini, A. and F. Franceschi, 1999. Autoimmune diseases and *Helicobacter pylori* infection. Biomed. Pharmacother., 53: 223-226.

Gasbarrini, A., E. Carloni, G. Gasbarrini and A. Ménard, 2003. *Helicobacter pylori* and extragastric diseases-Other Helicobacters. Helicobacter, 8 (Suppl. 1): 68-76.

Grigoriadou, S., A. Quraishi, J. Saravanna, V. Saravanan, C. Heycock and C. Kelly, 2002. What effect does *Helicobacter pylori* infection have on the risk of peptic ulceration in patients receiving NSAIDs for rheumatoid arthritis? Eur. J. Int. Med., 13: 269-273.

Harris, E.D., 1990. Rheumatoid arthritis. Pathophysiology and implications for therapy. N. Eng. J. Med., 322: 1277-1289.

Hess, G., 1997. Helicobacter infection: From diagnosis to treatment. J. Lab. Med. 21: 649-656.

Huang, S.S., A.K. Hassan, K.E. Choo, M.I. Ibrahim and T.M. Davis, 2004. Prevalence and predictors of *Helicobacter pylori* infection in children and adults from the Penan ethnic minority of Malaysian Borneo. Am. J. Trop. Med. Hyg., 71: 444-450.

Ishikawa, N., T. Fuchigami, T. Matsumoto, H. Kobayashi, Y. Sakai and H. Tabata *et al*., 2002. *H. pylori* infection in rheumatoid arthritis: Effect of drugs on prevalence and correlation with gastroduodenal lesions. Rheumatology, 41: 72-77.

Iwanczak, F., B. Iwanczak, T. Pytrus, O. Dworak G. Gosciniak and E. Vogtt, 2005. [Prevalence of *H. pylori* infection in the Polish child population.] Pol. Merkuriusz Lek., 18: 407-411.

Kikuchi, S., K. Yagyu, Y. Obata, L. Yingsong, H. Yatsuya, Y. Hoshiyama and T. Kondo *et al*, 2005. Serum pepsinogen values and *Helicobacter pylori* status among control subjects of a nested case-control study in the JACC study. J. Epidemiol., 15 Suppl 2: S126-S133.

Kim, N.Y., 2005. Epidemiology and transmission route of *Helicobacter pylori* infection. Korean J. Gastroenterol, 46: 153-158.

Koch, A., T.G. Krause, K. Krogfelt, O.R. Olsen, T.K. Fischer and M. Melbye, 2005. Seroprevalence and risk factors for *Helicobacter pylori* infection in Greenlanders. Helicobacter, 10: 433-442.

Kolacek, S., 2002. Specific aspects of *Helicobacter pylori* infection in childhood. Lijec Vjesn., 124 Suppl 1: 68-71.

Konturek, P.C. and E.G. Hahn, 2001. Extragastric manifestations of *H. pylori* infection. Z. Gastroenterol., 39: 311-320.

Kostaki, M., S. Fessatou and T. Karpathios, 2003. Refractory iron-deficiency anaemia due to silent *Helicobacter pylori* gastritis in children. Eur. J. Pediatr., 162: 177-179.

Kosunen, T.U., 1995. Antibody titres in *Helicobacter pylori* infection: Implications in the follow-up of antimicrobial therapy. Ann. Med., 27: 605-607.

Leandro Liberato, S., M. Hernandez Galindo, L. Torroba Alvarez, F. Sanchez Miramon, S. Leandro Ciriza, A. Gomez Abadia and P. Chueca Rodriguez, 2005. *Helicobacter pylori* infection in the child population in Spain: Prevalence, related factors and influence on growth. Ann. Pediatr (Barc), 63: 489-494.

McColl, K.E., L.S. Murray, D. Gillen, A. Walker, A. Wirz, J. Fletcher, C. Mowat, E. Henry, A. Kelman and A. Dickson, 2002. Randomised trial of endoscopy with testing for *Helicobacter pylori* compared with non-invasive *H. pylori* testing alone in the management of dyspepsia. Br. Med. J., 324: 999-1002.

McConkey, B. and R.D. Situnayake, 1988. Effects of rifampicin with and without isoniazid in rheumatoid arthritis. J. Rheumatol., 15: 46-50.

Mukherjee, P., B. Chacko, T. Singh, G. Pawar and H. Kaur, 2005. Prevalence of *Helicobacter pylori* infection in children with recurrent abdominal pain. Trop. Gastroentrol., 26: 102-104.

Negrini, R., L. Lisato, I. Zanella, L. Cavazzini, S. Gullini, V. Villanacci, C. Poiesi, A. Albertini and S. Ghielmi, 1991. *Helicobacter pylori* infection induces antibodies cross-reacting with human gastric mucosa. Gastroenterology, 101: 437-445.

Negrini, R., A. Savio, C. Poiesi, B.J. Appelmelk, F. Buffoli, A. Paterlini, P. Cesari, M. Graffeo, D. Vaira and G. Franzin, 1996. Antigenic mimicry between *H. pylori* and gastric mucosa in the pathogenesis of body atrophic gastritis. Gastroenterology, 111: 655-665.

Novak, J., Z. Szekanecz, J. Sebesi, A. Takats, P. Demeter, L. Bene, S. Sipka and Z. Csiki, 2003. Elevated levels of anti-*Helicobacter pylori* antibodies in Henoch-Schönlein purpura. Autoimmunity, 36: 307-311.

O'Dell, J.R., 1999. Is there a role for antibiotics in the treatment of patients with rheumatoid arthritis? Drugs, 57: 279-282.

Parente, J.M., D.A. Silva B.B., M.P. Palha-Dias, S. Zaterka, N.F. Nishimura and J.M. Zeitune, 2006. *Helicobacter pylori* infection in children of low and high socioeconomic status in northeastern Brazil. Am. J. Trop. Med. Hyg., 75: 509-512.

Perez, G.I., A.F. Cutler and M.J. Blaser, 1997. Value of serology as a noninvasive method for evaluating the efficacy of treatment of *Helicobacter pylori* infection. Clin. Infect. Dis., 25: 1038-1043.

Picco, P., M. Gattorno, M. Marchese, S. Vignola, M.P. Sormani, A. Barabino and A. Buoncompagni, 2000. Increased gut permeability in juvenile chronic arthritides. A multivariate analysis of the diagnostic parameters. Clin. Exp. Rheumatol., 18: 773-778.

Replogle, M.L., S.L. Glaser, R.A. Hiatt and J. Parsonnet, 1995. Biological sex as a risk factor for *Helicobacter pylori* infection in health young adults. Am. J. Epidemiol., 142: 856-863.

Rodrigues, M.N., D.M. Queiroz, J.G. Bezerra Filho, L.K. Pontes, R.T. Rodrigues and L.L. Braga, 2004. Prevalence of *Helicobacter pylori* infection in children from an urban community in north-east Brazil and risk factors for infection. Eur. J. Gastroenterol Hepatol., 16: 201-205.

Rodrigues, M.N., D.M. Queiroz, R.T. Rodrigues, A.M. Rocha, C.R. Luz and L.L. Braga, 2005. Prevalence of *Helicobacter pylori* infection in Fortaleza, Northeastern Brazil. Rev. Saude Publica, 39: 847-849.

Rybar, I., J. Rovensky, P. Masaryk, F. Mateicka and I. Revayova, 2004. Seroprevalence of *Helicobacter pylori* in rheumatoid arthritis and its relationship to pharmacotherapy. Vnitr. Lek., 50: 911-916.

Showji, Y., R. Nozawa, K. Sato and H. Suzuki, 1996. Seroprevalence of *Helicobacter pylori* infection in patients with connective tissue diseases. Microbiol. Immunol., 40: 499-503.

Silman, A.J. and J.E. Pearson, 2002. Epidemiology and genetics of rheumatoid arthritis. Arthritis Res., 4(suppl): S265-S272.

Singh, M., K.N. Prasad, S.K. Yachha, A. Saxena and N. Krishnani, 2006. *Helicobacter pylori* infection in children: Prevalence, diagnosis and treatment outcome. Trans. R. Soc. Trop. Med. Hyg., 100: 227-233.

Tilley, B.C., G.S. Alarcòn, S.P. Heyse, D.E. Trentham, R. Neuner and D.A. Kaplan *et al*, 1995. Minocycline in rheumatoid arthritis. A 48-week, double-blind, placebo-controlled trial. Ann. Int. Med., 122: 81-89.

Versalovic, J., 2003. *Helicobacter pylori* pathology and diagnostic strategies. Am. J. Clin. Pathol., 119: 403-412.

Weber, P., T. Brune, G. Ganser and K.P. Zimmer, 2003. Gastrointestinal symptoms and permeability in patients with juvenile idiopathic arthritis. Clin. Exp. Rheumatol., 21: 657-662.

Zentilin, P., V. Savarino, A. Garnero, S. Accardo and B. Seriolo, 1999. Is *Helicobacter pylori* infection a risk factor for disease severity in rheumatoid arthritis? Gastroenterology, 116: 503-504.

Zentilin, P., A. Garnero, L. Tessieri, P. Dulbecco, B. Seriolo, S. Rovida and V. Savarino, 2000. [Can *Helicobacter pylori* infection be a risk factor for the severity of rheumatoid arthritis?] Recenti Prog. Med., 91: 175-180.

Zentilin, P., B. Seriolo, P. Dulbecco, E. Caratto, E. Iiritano, D. Fasciolo, C. Bilardi, C. Mansi, E. Testa and V. Savarino, 2002. Eradication of *Helicobacter pylori* may reduce disease severity in rheumatoid arthritis. Aliment Pharmacol. Ther., 16: 1291-1299.