Effects of *Giardia lamblia* infestation on the clinical course of chronic hepatitis B

Giardia lamblia enfestasyonunun kronik hepatit B'nin klinik seyri üzerindeki etkileri

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SUMMARY: *To determine whether there was a role of concomitant giardiasis in chronic hepatitis B exacerbations in children, 46 patients with chronic hepatitis B and giardiasis were studied. In control group, there was 40 patients with chronic hepatitis B and no significant difference was found between the study and control groups with respect to age and sex (p>0.05).*

In the entire study period, toxic appearance and exacerbations were more frequently observed in study group (36.3% vs. 17.2% respectively; p<0.05). Also, the enlargement of liver in these patients was more marked and persisting. Recurrent abdominal pains and loose stool were two-fold frequent in study group (p<0.001). Children with giardiasis showed a tendency to decrease in erythrocyte and hemoglobin values. In addition, it was noted that there was a significant increase in erythrocyte sedimentation rate in these children. The level of ALT was 1.6 times higher and thymol test and gammaglobulin levels were 1.4 times in patients with giardiasis. Bilirubin levels appeared to be higher in study group and its return to normal levels was slower. More marked changes in cellular immunity were observed in children with giardiasis. Both the decrease in percentage of rosette-forming cells and the increase in ratio of TPR/TPS suggested the inhibition of cellular immunity in children with concomitant giardiasis. Mean duration of hospitalization in study group was longer than that of controls (p<0.01).

In conclusion, giardiasis is an important factor that has a certain aggravating effect on the clinical course of chronic hepatitis B. Its presence makes longer both the duration of return to normal levels of biochemical abnormalities and the duration of staying in the hospital. Consideration of an appropriate antiparasitic therapy in the treatment of children with chronic hepatitis may dramatically improve the course of the disease.

Key words: Chronic hepatitis B, giardiasis

ÖZET: *Konkomitan giardiasis enfestasyonunun kronik hepatit B alevlenmeleri üzerinde rolü olup olmadığını araştırmak amacıyla gerçekleştirilen bu çalışmaya kronik hepatit B ve giardiasis bulunan 46 çocuk alındı. Kontrol grubunda giardiasis bulunmayan 40 kronik hepatit B olgusu mevcuttu. İki grup arasında yaş ve cinsiyet açısından fark saptanmadı (p>0.05).*

Tüm çalışma döneminde giardiasisli olgularda toksik görünüm ve alevlenmeler daha fazla sıklıkta izlendi (sırasıyla % 36.3 ve % 17.2; p<0.05). Yine bu grupta karaciğerdeki büyüme daha fazla ve normale dönme süresi daha uzundu. Ayrıca, tekrarlayan karın ağrıları ve yumuşak dışkılama iki kat daha fazla sıklıkta gözlendi (p<0.001). Giardiasisli çocuklarda eritrosit ve hemoglobin düzeylerinde azalma eğilimi mevcuttu ve sedimentasyon hızı belirgin olarak artmıştı. ALT düzeyleri 1.6 kat ve timol testi ve gamaglobulin düzeyleri 1.4 kat daha yüksek bulundu. Bilirubin düzeyleri daha yüksek ve normale dönüş süreleri daha uzundu. İmmünite ile ilgili veriler incelendiğinde, giardiasisli olgularda sellüler immünite göstergelerinde daha belirgin değişiklikler saptandı. Rozet-oluşturan hücrelerin oranındaki azalma ve TPR/TPS oranındaki artma giardiasisli çocuklarda immünitenin baskılanmış olduğunu düşündürdü. Çalışma grubunda ortalama hospitalizasyon süresi kontrollere göre daha uzundu (p<0.01).

Sonuç olarak, giardiasis, kronik hepatit B enfeksiyonunun klinik seyri üzerinde agrave edici etkisi bulunan ve hem biyokimyasal bozuklukların normale dönme süresini hem de hospitalizasyon süresini uzatan önemli bir faktördür. Kronik B hepatitli çocukların tedavisinde antiparazitik tedavi seçeneğinin de göz önünde bulundurulması hastalığın seyrini önemli ölçüde değiştirebilir.

Anahtar sözcükler: Kronik B hepatiti, giardiasis

The clinical course of viral hepatitis combined with giardiasis is marked by frequent exacerbations (1-4).Giardiasis has a significant influence on the children's general health status, by reducing particularly the immune reactivity (5). In many cases, giardiasis is appeared to be responsible from the chronic pathologic processes in the gastrointestinal tract (6, 7). Symptoms are more frequent and severe in children younger than 5 years old in whom treatment is the least satisfactory (2, 7). Although the understanding of etiology of hepatitis infection is increasingly growing, the relationship between such different pathogens as *Giardia lamblia* and hepatitis B virus remains unclear. This study was carried to determine whether there was a role of concomitant giardiasis in chronic hepatitis B exacerbations in children.

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METHODS

Forty-six children with chronic hepatitis B and concomitant giardiasis that applied to Hepatology Department of Scientific Research Institute of Pediatrics in Tashkent were included to study. Of these patients, persistent hepatitis B was diagnosed in 26 (56.5%) cases and chronic active hepatitis B in 20 (43.5%). There was 22 (47.8%) female and 24 (52.2%) male in this study group; mean age was 5.6 ± 2.1 years (range 4-7 years).

In control group, there was 20 (50.0%) children with persistent hepatitis B and 20 (50.0%) with chronic active hepatitis B. Of these 40 patients, 21 (52.5%) female and 19 (47.5%) male, mean age was estimated as 5.1 ± 2.3 years (range 3-7 years). No significant difference was found between the study and control groups with respect to age and sex ($p>0.05$).

The diagnosis of chronic hepatitis B was established on the basis of laboratory evidences (liver function tests as well as the results of HBsAg, anti-HBs, HBeAg, anti-HBeAg and anti-HBc studies). For the diagnosis of giardiasis, duodenal contents taken with intubation was examined for trophozoites.

Metronidazole 15 mg/kg/day in 3 divided doses for 5 days was used to treat the children with giardiasis.

In statistical analysis, student-t and Fisher's exact chi-square test were used. Results were shown as mean ± standard deviation (SD). $p(a)=0.05$ was considered as significance level.

RESULTS

In the entire study period, toxic appearance and exacerbations were more frequently observed in children with chronic hepatitis and giardiasis comparing to controls (36.3% vs. 17.2% respectively; $p<0.05$). General weakness was noted in 51.4% of patients in the study group and in 31.2% of controls ($p<0.05$). Similarly, pallor was observed in rates of 57.6% and 45.4% respectively ($p<0.05$).

Comparing to control group, recurrent abdominal pains and loose stool were two-fold frequent in children with chronic hepatitis and giardiasis ($p<0.001$). Nausea was observed in 40.1% and 25.4% of children in study and control groups respectively ($p<0.05$), abdominal distention in 35.7% and 10.3% ($p<0.01$). Fifteen percent of patients in the study group complained about constipation. Additionally, anal pruritus was detected in all cases with giardiasis.

Table 1. Comparison of biochemical findings obtained in two groups

	Study group (n=46)	*Control group (n=40)*	*p*
T. bilirubin (mmol/L)	23.6 ± 2.9	14.7 ± 1.7	<0.05
ALT (mmol/L)	2.57 ± 0.23	1.56 ± 0.13	<0.05
AST (mmol/L)	1.33 ± 0.11	1.10 ± 0.14	>0.05
Thymol test (U)	9.95 ± 0.48	7.05 ± 0.90	<0.05
Total protein (g/L)	58.4 ± 2.3	66.2 ± 2.1	>0.05
Albumin (%)	41.9 ± 1.2	48.3 ± 1.1	>0.05
Gammaglobulin (%)	31.0 ± 1.2	22.8 ± 1.5	<0.05

In 10.2% of children with chronic hepatitis and concomitant giardiasis, rashes in form of urticaria was noted, such changes were not observed in control group ($p<0.05$). Similarly, vascular changes such as marked network of venous collaterals on the skin of chest and abdomen were more frequently observed in cases with giardiasis comparing to control group (21.4% vs. 8.3%; $p<0.01$).

The enlargement of liver in patients with chronic hepatitis and giardiasis was more marked and persisting. Mean increase in liver size was determined as 3.5 ± 0.6 cm and 7.2 ± 1.4 cm in study and control groups respectively ($p<0.05$). Also, incidence of subicteric appearance was higher in patients with giardiasis (11.5% vs. 5.0%; $p<0.05$). There were no differences in spleen size between both groups.

Children with giardiasis showed a tendency to decrease in erythrocyte and hemoglobin values. In addition, it was noted that there was a significant increase in erythrocyte sedimentation rate in these children (mean 30.4 ± 4.1 mm/h vs. 16.7 ± 3.0; $p<0.05$). In the study group, neutrophilia in differential count was found in eight patients and basophilia in two, while in control group there were no such changes. Further, an increased ratio of eosinophils (5%) in peripheral blood was observed in 70.4% of patients with giardiasis and in four of these children, percentage of eosinophils was higher than 10%.

When liver function tests were compared, the level of ALT was 1.6 times higher and thymol test and gammaglobulin levels were 1.4 times in patients

Table 2. Comparison of findings about cellular immunity in two groups

	Study group (n=46)	*Control group (n=40)*	*p*
T-lymphocytes	34.5 ± 1.0	47.6 ± 1.0	<0.05
B-lymphocytes	35.8 ± 0.9	31.4 ± 1.0	>0.05
TPR R-RFC	30.1 ± 1.1	35.5 ± 1.1	<0.05
TPS E-RFC	4.9 ± 0.4	11.1 ± 0.8	<0.01
TPR/TPS	7.1 ± 0.6	3.6 ± 0.3	<0.05

with chronic hepatitis combined with giardiasis compared to controls (Table 1). Hyperbilirubinemia in various degrees of severity was determined in all the patients. However, bilirubin levels appeared to be higher in study group and its return to normal levels was slower.

In comparison of immune status in two groups, more marked changes in cellular immunity were observed in children with chronic hepatitis with giardiasis (Table 2). Both the decrease in percentage of E-RFC (rosette-forming cells) and the increase in ratio of TPR/TPS suggested the inhibition of cellular immunity in children with concomitant giardiasis.

Mean duration of hospitalization in study group was 36.2 ± 4.5 days and it was found as 19.6 ± 2.7 days in controls ($p<0.01$).

DISCUSSION

Giardiasis is an infection of the small intestine caused by *Giardia lamblia*, a flagellated protozoan. It is often asymptomatic, but clinical manifestations may range from flatulence to malabsorption (1, 8, 9).

The infection is found worldwide, especially in children and particularly where sanitation is poor; rates > 50% have been noted in day-care centers. Infection rates are also high among travelers, male homosexuals, and patients with gastrectomies, decreased gastric acidity, chronic pancreatitis, and immunodeficiencies. In the USA, giardiasis is one of the most common intestinal infections; about 7% of stools submitted for parasitologic examination contain *G. lamblia* cysts (10).

The *G. lamblia* trophozoite attaches itself to the duodenal and jejunal mucosa by a ventral sucker; it multiplies by binary fission. The organisms are passed in normal stool as cysts. In this resistant form, the disease is spread from host to host by fecal-oral routes, either directly (as between children or sexual partners) or indirectly (via food or water). Both humans and wild animals may serve as reservoirs.

Symptoms are commonly mild, but intermittent nausea; eructation; flatulence; epigastric pain; abdominal cramps; bulky, malodorous stools; and diarrhea may occur. In severe cases, malabsorption can lead to significant weight loss. The severity of the malabsorption is related to the degree of infection, but the pathogenesis of these manifestations is unknown. Mechanical blockade of the microvilli, damage to their brush border, altered motility, and mucosal invasion resulting in T-cell-mediated mucosal damage have all been suggested as possible mechanisms (11).

Finding the organism in the stool or duodenal secretions is diagnostic. In acute infections, the parasite can be readily found in the stool; in chronic cases, excretion is irregular, requiring repeated stool examination. Alternatively, duodenal contents can be examined for trophozoites as being in our study.

Metronidazole is an effective treatment for the infestation and in our study, it was well tolerated in all cases. Clinical symptoms may be improved with the application of such an active antiparasitic therapy as well as liver function tests normalized. Control studies of duodenal contents did not reveal *G. lamblia* in any patients. Efficacy of treatment of patients with chronic hepatitis and concomitant giardiasis depends on early detection of parasitic invasion and timely application of antiinflammatory and antiparasitic therapy (12).

In a study of Sotto et al., hepatic functional tests and hepatic biopsy were performed in 25 patients with giardiasis diagnosed by duodenal intubation (13). Alterations of hepatic histology were detected in 60% of patients (36% steatosis and 24% inflammatory lesions). In addition, chronic persistent hepatitis was found in three cases and chronic active hepatitis in two. Some degree of regression of hepatic lesions was reached only with antiparasitic treatment and in some cases, reappearance of lesions was observed related to reinfestations. At the end of paper, authors emphasized the importance to dismiss giardiasis and to

treat it before to undergo any other therapeutic behavior for every patient with histologic diagnosis of chronic hepatitis without viral markers.

In conclusion, giardiasis is an important factor that has a certain aggravating effect on the clinical course of chronic hepatitis B. Its presence makes longer both the duration of return to normal levels of biochemical abnormalities and the duration of staying in the hospital. Consideration of an appropriate antiparasitic therapy in the treatment of children with chronic hepatitis may dramatically improve the course of the disease.

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