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Burden of parasitic infection and its impact on growth of children with hepatitis C Virus

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Abstract

Background: Egypt showed high infection rates of intestinal parasites especially in the rural areas. Children suffering of HCV are considered immunocompromised which makes them vulnerable to a wide spectrum of parasitic infections. The aim of the study is to assess the impact of different protozoa and helminthes infection on growth of children with hepatitis C virus infection (HCV).

Materials and methods: This study was conducted at National Hepatology and Tropical Medicine Research Institute, Cairo, Egypt and included 115 children who proved to have HCV infection by PCR. In addition, 144 non-HCV infected children were enrolled as control group. Both groups were clinically assessed and investigated for the presences of parasites infestation and their effects on growth in **HCV** infected children.

Results: Percentage of helminthes' infection in the HCV infected children's was significantly higher than that of the control group (P = 0.001). Parasitic infections have negative impacts on growth in HCV infected children. In HCV children co-infected with parasites, the weight and height percentiles were significantly lower compared to those HCV infected group without parasitic infection (P = 0.001, 0.002; respectively). In HCV-infected groups, there was a significant positive correlation of albumin with weight percentile (r = 0.318 and p= 0.000) and height percentile (r = 0.316 and p= 0.000).

Conclusions: Children with hepatitis C virus infection are vulnerable to parasitic infections. Parasitic co-infection of HCV affected children has a negative impact on their growth and general health.

Introduction

Hepatitis C virus (HCV) is a disease that may lead to serious effects in the liver; therefore, any associated medical problems would be considered an additional burden [1]. Unfortunately, approximately 70% of acute HCV infections become chronic [2], which may result in a continuum of inflammation and eventually cirrhosis [3].

The GT-4 and its subtype 4a constitute the vast majority of HCV infected cases in Egypt [4]. HCV is a real challenging medical problem in children. The prevalence of HCV infection in children aged 0-18 years is estimated to be 0.13% [5, 6]. Approximately, half of the affected children have active manifestations [7].

In children, HCV infection has multiple negative impacts; not only physically but on the quality of life, psychosocial aspects and cognitive functions [8, 9]. In Egypt there is a high infection rate of intestinal parasites especially in the rural areas [10]. Children suffering of HCV are considered immunocompromised which makes them vulnerable to a wide spectrum of parasitic infections, especially in a non-hygienic environment and lack of sanitation measures [11]. Parasitic (helminths and protozoal) infections may lead to variety of medical problems such as irritable bowel syndrome, chronic fatigue syndrome, food allergies, colic, anorexia, abdominal distension, anxiety and reactive arthritis [12], iron-deficiency anemia, malnutrition, growth failure and disturbance of cognitive functions [13]. Moreover, many of the helminths and protozoa may reach the liver causing direct hepatic tissue injury, inflammation and abscess formation [14-16].

The aim of the study is to assess the impact of different protozoa and helminthes infection on growth of children with hepatitis C virus infection.

Materials and methods

This was a cross-sectional study that conducted at National Hepatology and Tropical Medicine Research Institute (NHMRI) during the period from February 2019 to March 2020. The study included 115 children, aged between 3- 14 years, who were proved to have HCV infection, but did not start any treatment yet to eradicate HCV infection (they have not been enrolled, at the time of the study, for treatment protocol yet). In addition, 144 children free from HCV infection with cross matching age and sex as a control group.

The study excluded other proved HCV infected children suffering from additional comorbid conditions or diseases such as renal or cardiac problems and also excluded those with abnormal coagulation profile. The study was approved by Ethical committee of the General Organization for Teaching Hospitals and Institutes (GOTHI). Written, verbal consents were taken from each patient by parent/parents or guardians.

Each child was subjected to the following.

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- **Questionnaire.** Parents of each child was subjected to the following; Name, age, gender, level of education, socioeconomic status, source of drinking water, sewage disposal system, complaint, fever, vomiting, type of diarrhea, associated fecal blood /mucous.
- **Physical and Abdominal U.S examinations.**
- **Weight and height percentile assessment according to the Egyptian growth charts [17].**
- **Laboratory investigations.**

Samples collection (Blood and stool)

Blood sample.

- 5 ml of peripheral venous blood in a vacutainer tube containing EDETA for CBC and molecular diagnosis of HCV. In addition, 2 ml of peripheral venous blood in a vacutainer tube containing sodium citrate for detection prothrombin time (PT) and International Normalized Ratio (INR) test.
- 3 ml of peripheral venous blood in a plane vacutainer tube for assessment of liver functions, parasite detection in blood and HCV antibodies

Stool sample.

Fresh stool sample was collected in a dry, clean sterile, labeled container, each was divided into four sub samples,1st sub sample prepared by direct smear, the 2nd subsample prepared by concentrator tubes, the 3rd subsample was examined by Kato-Katz method and 4th subsample for Copro antigens detection (all subsamples were examined immediately without delay).

Laboratory investigations.

1- *Assessment of liver functions.*

Bilirubin, alanine transaminase (ALT), aspartate aminotransferase (AST), albumin, and coagulation profile were assessed.

2- *Complete blood count (CBC).* To assess hemoglobin percentage (Hb %) and diagnose anemia.

3- *Diagnosis of HCV.*

- HCV antibodies: Using commercially available kits by BioTina GmbH (Rapid test), D-79112 Freiburg-Germany.
- Quantitative PCR for HCV detection: Molecular detection (Real time PCR) using commercially available kits by Qiagen, Germany on QIA symphony /roter crème system. The lower detection limit is 15 IU/mL.

4. *Diagnosis of parasitic infection.*

- Serologic examination: By Indirect Haemagglutination Test (IHA) using commercially available kits by FUMOZE DIAGNOSTICS - FRANCE. Test procedures and interpretation guided by manufactures instructions as the following: For Schistosomiasis, titer 1: 160 indicates significant reaction, with presumption of acute infection. For Fascioliasis, titer 1: 320 indicates significant reaction in favor of acute infection. For Amoebiasis, titer 1; 160 indicates a significant reaction in favor of visceral amoebiasis.

Stool analysis.

- Macroscopic stool examination. Visible blood, mucous, pus, larvae, worms and the consistency were detected.
- Microscopic stool examination. Using direct smear stained with Lugol iodine Paraseb concentrator tubes on FE5 FECAL AUTOMATED PARASITIC WORK STATION and by Kato -Katz techniques.
- For identification of parasitic eggs, larvae, cysts, trophozoites. Copro Antigens detections: - For Entamoeba Histolytica, Giardia lamblia and Cryptosporidium antigens using commercially available kits by COMBI- RIDA SCREEN, N 1712, BIOPHARMA, GERMANY. Immunochromatographic quantitative rapid quick test.

Statistical analysis

Statistical analysis was carried out using SPSS v22.0 IBM statistical package for social science. Categorical data were subjected to descriptive analysis using frequency and percentage, while scale data was described as s mean, standard deviation (SD) and range. Tests for inferential statistics of two groups were chi square test, independent t test, while ANOVA was used to compare multiple means of scale variable, followed by LSD test. The correlation of parametric data was done using Pearson correlation, while nonparametric data using Spearman; s rho test. The significance level was set to $P < 0.05$.

Results

The study included 115 children (58 males and 57 females), with mean age 7.43 ± 2.64 years, who proved to have HCV infection by PCR, in addition to 144 normal children (70 males and 74 females), their mean age was 7.75 ± 2.65 years to serve as a control group. The HCV-infected group was further divided into HCV-infected group without parasitic co-infection (group 1A) and HCV-infected group with parasitic co-infection (group 1B). The normal control (HCV-negative) second group was further divided into control group without parasitic infection (group 2A), and control group with parasitic infection (group 2B).

T**able1** depicts the clinical and radiological data. There was no significant difference as regards, sex, age, abdominal pain and diarrhea however, vomiting was significantly more frequent in the HCV-infected group, compared to control group (p= 0.046). Abdominal ultrasonography of the HCV-infected cases showed homogenous liver texture with non-reported splenomegaly or ascites in any case. Normal hepatic structure and texture was reported in the majorityof HCV-infected cases (92/ 115; 80 %), mild hepatomegaly was observed in 17 HCV-infected cases (14.8 %), while only 6 cases (5.2 %) showed decrease in their liver size.

There was no significant difference as regards, protozoa infection between both studied group, however, the percentage of helminthes infection in the HCV-infected group was significantly higher than that in the control group (p= 0.001) **(Table 2)**.

Table 3 shows, the distribution of weight and height percentiles changes among the studied groups. A general decrease in growth rate, in terms of weight and height percentile, is evidenced in HCV-infected group with parasitic affection (group1B) where was, all weight percentiles were significantly lower than those in (group 1A) (p = 0.001). The distribution of the weight percentiles

in the HCV-infected cohort with parasites (group1B) showed that, the highest percentage (26%) of the weights of less than 25th percentile (19/73), compared to 7.14% from HCV-infected cohort without parasites (group 1A) (3/42); this comparison was significant (p=0.001). Moreover, the comparison with the corresponding control group with parasites group 2B revealed 7.7% (5/65) of the weights of less than 25th percentile; this comparison was significant (p=0.000). Moreover, the weights of 25th – 50th percentile was nearly equal in both groups 1A (25/42; 59.5%) vs 1B (43/73; 58.9%). Furthermore, the weights of 50th -75th and more than 75th percentile were the least in the HCV-parasite co-infected group 1B, compared to the rest of the groups (11/73; 15%) this comparison was significant (p=0.00). Also when we compared HCV-infected cohort without parasites group (1A) to healthy controls without parasites group (2 A), growth was significantly affected (p=0.000) showing the adverse effect of HCV infection on the children weight gain. In a similar pattern, the height percentiles were significantly reduced in group 1B, compared to group 1A (p = 0.002). The heights of less than 25th percentile was 23.3% (17/73) in group 1B, compared to 9.5% (4/42) in group 1A **(** p=0.002); and 1/79 (1.3%) in control group without parasites (group 2A) compared to control group with parasites (group 2B) (1/65; 1.5%, (p= 0.002). Moreover, the heights of 25th – 50th percentile was (37/42; 88%) in group 1A versus (45/73; 61.6%) in group 1B. Theses finding confirm the negative impact of parasitic infection on the growth rate in HCV infected cohort. Also when we compared HCV-infected cohort without parasites group (1A) to healthy controls without parasites group (2A), height was significantly affected (p=0.002) showing the adverse effect of HCV infection on the children height increase.

As shown in **table 4,** there was no significant change as regard the serum bilirubin level among all studied groups. There was a significant increasing as regard, ALT level and a significant decreasing in hemoglobin and serum albumin in group 1B versus other studied groups**.** Also, a significant decreasing in in hemoglobin and serum albumin in group 1A versus group 1B was found. Furthermore, AST level was significantly increased in group 1B in comparison to Group 2B with parasitic infection and also in group 1A versus group 2 A with non-significantly difference between group 1A versus Group 1B (0.085). In both HCV-infected groups, there was a significant positive correlation of albumin with weight percentile (r = 0.318 and p = 0.000), height percentile (r = 0.316 and p= 0.000). Moreover, there was a positive non-significant correlation between hemoglobin concentration and weight percentile (r = 0.19, p = 0.766) and negative non- significant correlation between hemoglobin concentration and height percentile (r = -0.031, p = 0.622) **(Table 5)**.

Table 1. Clinical and radiological data in HCV cases and control group.

Parameters	Group 1 HCV infected	Group 2, Healthy control	p- value
Number	115	144	
Gender (M/F)	58/57(50.4%/49.6%)	70/74 (48.6% /51.4%)	p= 0.771
Age/y	7.43 ± 2.64	7.75 ± 2.65	p=0.329
Abdominal pain	59 /115 (51.3 %)	75 /144 (52.1 %)	p= 0.901
Diarrhea	44/115(38.3 %)	43 / 144 (29.9 %)	p= 0.155
Vomiting	21 /115 (18.3 %)	14/ 144 (9.7 %)	p= 0.046
Abdominal US findings			
Normal	92/115 (80 %)	144/ 144 (100%)	p = 0.00
Hepatomegaly	17/115 (14.8 %)	0	
Shrunken	6/115 (5.2 %)	0	

Table 2. Parasitic infection incidence in HCV cases and control group.

Parameters	Group 1 HCV infected (115)	Group 2 control (114)	p- value
Protozoa			
Entamoeba histolytica (E.H)	19/115 (16.5 %)	24/144 (16.7 %)	
Giardia lamblia (G.L)	13/115 (11.3 %)	18/144 (12.5%)	
E.H + G.L	2 /115 (1.73 %)	0	
Total protozoa	34 /115 (29.5 %)	42/ 144 (29.1 %)	X^{2} = 2.58 p= 0.46

	Helminthes		
Enterobius vermicularis	6/115 (13.9 %)	16/ 144 (11.1 %)	
Hymenolepis Nana	9/115 (7.8 %)	7/144 (4.9%)	
Heterophyes heterophyes	6 /115 (5.2%)	-	
Schistosoma haematobium	4 /115 (3.5%	-	
Schistosoma mansoni	3 /115 (2.6%)	-	
Taenia saginata	1/115 (0.9%)	-	
Total helminthes	39/115 (33.9 %)	23/144 (16 %)	$X^2 = 23.202$ p= 0.001

Table 3. The gender and anthropometric parameters of both groups; in infected HCV pediatric cases compared to their control groups.

Parameters	**Group 1: HCV infected children**		**Group 2: Healthy control children**		**p-value**
	Group 1A without parasitic infection	Group 1B **with** parasitic infection	Group 2 A without parasitic infection	Group 2B **with** parasitic infection	
Number	42	73	79	65	
Gender(M/F)	22/20	36/37	38/41	32/33	$X^2 = 0.204$ P= 0.977
Age /y	7.86± 2.3	7.18± 2.8[a]	2.6 ±0.29	2.7 ±0.33[b,c]	[a] 0.187 [b] 0.229 [c] 0.912 [d] 0.169
			Weight percentile		
< 25th percentile	3/42 (7.14%)	19/73 (26%)	1/79 (1.26%)	5/65 (7.7%)	[a] 0.001 [b] 0.000 [c] 0.000 [d] 0.000
25th – 50th percentile	25/42 (59.5%)	43/73 (58.9%)	30/79 (37.97%)	38/65 (58.5%)	
50th -75th percentile	13/42 (30.9%)	11/73 (15%)	44/79 (55.69%)	22/65 (33.8%)	
>75th percentile	1/42 (2.4%)	0	4/79 (5%)	0	
			Height percentile		
< 25th percentile	4/42 (9.5%)	17/73 (23.3%)	1/79 (1.3%)	1 /65 (1.5%)	[a] 0.002 [b] 0.000 [c] 0.002 [d] 0.002
25th – 50th	37/42 (88%)	45/73 (61.6%)	57/79 (72.15%)	64/65 (98.46%)	
50th -75th	0/42	11/73 (15%)	20/79 (25.3%)	0/65	
>75th percentile	1/42 (2.38%)	0	0	0	

Results are means ± SDM; comparisons are done; ([a]) Group 1A compared to group 1B; ([b]) Group 1B compared to group 2B; ([c]) Group 2B compared to group 2A; (d) Group 1A compared to group 2A.

Table 4. The laboratory parameters; of studied groups.

Parameters	Group 1: HCV infected children		Group 2: Healthy control group		p-value
	Group 1A without parasitic infection	Group 1B with parasitic infection	Group 2 A without parasitic infection	Group 2B with parasitic infection	
Bilirubin (mg/dL)	0.75 ± 0.49	0.66 ± 0.56	0.59 ± 0.28	0.71 ± 0.8	[a] 0.408 [b] 0.61 [c] 0.218 [d] 0.469
ALT (U/L)	39 ± 27.6	46.8± 31.25	23.15 ± 5.59	21.98 ± 6.5	[a] 0.05 [b] 0.000 [c] 0.734 [d] 0.000
AST (U/L)	34.8 ± 25.2	41.02± 27.9	24.36 ±5.8	21.46 ±5.97	[a] 0.085 [b] 0.000 [c] 0.349 [d] 0.000
Hb (%)	11.74 ± 1.97	10.9 ± 2.14	12.3 ± 2.15	11.65 ± 2	[a]0.043 [b] 0.04 [c] 0.072 [d] 0.000
Albumin (g/mL)	4.02 ± 1.07	3.42 ± 1.24	4.4 ± 0.58	4.2 ± 0.73	[a] 0.001 [b] 0.000 [c] 0.209 [d] 0.000

Results are means ± SDM; comparisons are done; ([a]) Group 1B compared to group 1A; ([b]) Group 1B compared to group 2B; ([c]) Group 2B compared to group 2A; (d) Group 1A compared to group 2A.

Table 5. Correlations between serum albumin and hemoglobin concentration with weight percentile and height percentile in chronic hepatitis C infection.

	Serum albumin r:p	hemoglobin concentration r:p
Weight percentile	0.318: 0.000	0.19: 0.766
Height percentile	0.316: 0.000	-0.031: 0.6220

Discussion

Many of the children with HCV infection are asymptomatic similar to infected children with parasitic infestations. The synergistic disease burden of both infections in children deserves special medical attention from pediatricians. The current research highlights the importance of investigating the additional deleterious impact of parasitic infections in HCV-infected children in Egypt, in an attempt to unveil the hidden dangers and highlight the negative impacts of both infections. HCV infection is known for its chronic course that consequently may lead to liver damage. Therefore, when associated with parasitic infestations, HCV infection would lead to additional adverse effect on the immunity of HCV infected children. Our study demonstrated that, the incidence of protozoal infection was similarly observed in both HCV infected patient group and their control counterparts, however, the percentage of helminthes infection in the HCV infected patient group was significantly higher than that in the control group. This finding comes in contrast to other studies found that, the majority of intestinal parasitic gastrointestinal infections in Egypt is caused by protozoa (57.6%); whereas helminthes were found only in 9.9% of infected cases1[18]. This controversy can be explained by the disturbance of the immunity of the patients due to chronic affection of the liver pathology resulting in significant increase in the incidence of helminthes in HCV infected cases compared to their control counterparts [19]. Moreover, some uncommon helminthes were only detected in the

HCV-diseased group such as Heterophyes heterophyes, Schistosoma mansoni, Schistosoma haematobium and Taenia saginata.

As regards gastrointestinal manifestations, the statistical comparison revealed a significant difference between both groups regarding associated vomiting that was more among the HCV-infected group. The reported vomiting may be attributed to the HCV infection itself due to the anticipated correlation with increase in HCV viral load as suggested previously [20], or due to the drugs ingestion [21]. Other gastrointestinal symptoms, such as diarrhea and abdominal pain were similarly observed in both investigated groups.Regarding the growth rate that is evaluated by the weight and height percentiles, both were significantly lower in most of the HCV-infected patients group, compared to their control group. The highest number of patients with weight and height of less than 25% percentile were observed in the HCV- group co-infected with parasites. In the same pattern the lowest percentage of the weights of 50th -75th and more than 75th percentile were the least in the HCV-parasite co-infected group, compared to the rest of the groups. This was also observed by Kamal and colleagues, who found that children infected with HCV showed impaired growth rate [22]. Some authors attributed this growth delay to the concomitant negative impacts of HCV burden on the children due to poor quality of life and compromised nutritional status as well as low socio-economic status of their families [23]. Coinciding with other authors [24], we found that parasitic infections affected the children's growth rate. Intriguingly, the growth percentiles were markedly affected by the parasitic infestations in the HCV infected cases as well as the normal control groups.

In alignment with the growth rate, the laboratory, biochemical results revealed a general decrease in hemoglobin concentration in both investigated groups, but is significantly lower in both HCV- parasite co-infected group (group 1B) and control group infected with parasites (group 2 B); as shown in table 3. The prominent anemia, which was proved to be iron deficiency anemia reflects the poor nutritional status of the children. This can be attributed to the low socioeconomic standards and associated chronic infection with HCV and also additional parasitic infestations [25].

Albumin is considered a marker of liver synthetic function and nutritional status as well[26]. Its level was lower in HCV- parasite co-infected group, compared to HCV-infected group without co-infection with parasites, indicating the adverse effect of parasites when associated with HCV infection. This marked decrease can be attributed to the associated poor nutritional status associated with HCV infection. Moreover, the concomitant parasitic infections can cause disturbance in the digestion and absorption of food, which can also cause Hypoalbuminemia. The decreased albumin concentration, also be rationalized by the chronic inflammation and subsequent loss of nutrients due to associated enteropathy and /or eosinophilic gastritis[27]. Moreover, the induced Hypoalbuminemia may be due to loss of albumin in urine (albuminuria) due to glomerulonephritis that follows chronic hepatitis caused by HCV infection[28]. Intriguingly, the evidenced decrease in albumin was also positively correlated with significant decrease of weight percentile, height percentile and Hb%. This coincides with the findings of others, who found that, in children with chronic liver diseases, malnutrition was correlated with growth failure that was associated with hypoalbuminemia [29].

As for the liver enzymatic functions, ALT was significantly elevated in HCV- parasite co-infected group, compared to HCV-infected group without co-infection with parasites. This may indicate further liver damage due to the associated possible deleterious effects of parasites. This coincides with the opinion of other authors who stated that increase of the liver enzymes level may denote ongoing hepatic tissue damage [30]. There are some limitations of the current research, a relative small sample size and a FibroScan was not done for investigation of the degree of fibrosis in HCV infected group, but would be of more value to correlate between the degree of fibrosis and incidence of parasitic infestations.

Conclusion

Children with HCV are vulnerable to protozoal and helminthes infections that have an adverse effect not only on their general health status and growth potentials but also cause significant disturbance of the liver functions. It is strongly recommended that in all children with HCV, a thorough investigation on the anticipated infestation with protozoa and helminthes and to be appropriately treated and eradicated. Further larger scale studies are recommended in order to provide greater statistical reliability.

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