Is Hepatitis C Virus Infection Common in Pediatric Patients with Persistent and Chronic Immune Thrombocytopenia?

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ABSTRACT:

Background: Immune thrombocytopenia (ITP) is an autoimmune, acquired disease characterized by transient or persistent thrombocytopenia. ITP, mostly self-limiting, is also known to occur in association with bacterial and viral infections. Egypt, had one of the highest burdens of Hepatitis C Virus (HCV) infections globally.

Methods: Pediatric patients with persistent and chronic ITP were evaluated for evidence of HCV infection. HCV antibody test (by ELISA) was performed for all patients. HCV PCR test was done for patients with positive antibody test.

Results: Eighty-seven patients were enrolled, with M/F ratio of 1.3:1. HCV antibody test was positive in 8 patients (9%), and only one of them had Positive HCV PCR. Different parameters (age, gender, initial presenting symptoms, disease duration, bleeding grade, transfusion of blood products, treatment type and response to treatment) showed no statistically significant difference between HCV antibody positive and HCV antibody negative cases.

Conclusions: HCV infection is not a common comorbidity among our cohort of pediatric patients with persistent and chronic ITP. No significant difference was detected between HCV antibody positive cases and HCV antibody negative cases as regards clinical presentation, or response to treatment..

1. Introduction

Immune thrombocytopenic purpura (ITP) is an autoimmune disease characterized by thrombocytopenia due to antibodies against the platelet antigens, which result in platelet destruction in the reticuloendothelial system and decreased production [1].

ITP, is considered to be an acquired, mostly self-limiting disease [2]. It is also known to occur in association with bacterial and viral infections [3]. Chronic infections are typically associated with long-lasting ITP, thus leading to the persistence of chronic ITP. [4] Among the viral infections, Hepatitis C virus (HCV) is considered to be the most immunogenic virus reported to persist in association with high autoimmunity, namely the increased incidence of auto-antibodies such as anti-nuclear and anticardiolipin antibodies and rheumatoid factor [5].

The HCV infections pose a significant public health concern and in pediatric populations, is estimated to be around 3.5–5 million. The prevalence is about 0.3% and 0.4% in high-income countries and low-income countries respectively [6]. Egypt it is known to have the highest HCV prevalence worldwide, according to the Egyptian Demographic and Health Surveys showed that HCV prevalence in those aged < 15 years was 0.4% [7].

HCV has been reported to be associated with the occurrence of autoimmune disorders, including ITP [**Error! Bookmark not defined.**]. Auto-antibodies are commonly found in up to 40% cases of chronic

HCV infection [8]. High-affinity binding of HCV to platelet membranes and the subsequent binding of anti-HCV antibodies to platelets, theoretically, leads to increased phagocytosis of platelets. Of special relevance is the improvement of thrombocytopenia following successful Interferon (INF) therapy in HCV-infected patients [9].

The treatment of HCV-Related ITP; steroids cause an elevation of hepatic transaminases, HCV viral load and elevated serum bilirubin concentrations, IVIG was documented to be effective in increasing platelet counts in both HCV seropositive and HCV-seronegative patients, and IFN was proved to be efficient in decreasing HCV RNA in correlation with a significant increase of thrombocytes in HCV-positive adult patients with ITP [10].

The current study aimed to estimate the prevalence of HCV infection among pediatric patients with persistent and chronic ITP who are treated at Pediatric Hematology Department, Cairo University Children Hospital (CUCH), Egypt. In addition, the study aimed to evaluate platelet counts in HCV-positive patients in comparison to HCV-negative patients, and to assess efficacy of different treatment options in patients with persistent and chronic ITP (HCV-positive).

MATERIALS AND METHODS

Study design

This study included all pediatric patients less than 18 years diagnosed as persistent or chronic ITP at the Pediatric Hematology Outpatient Clinic, CUCH during the period from December 2019 to June 2021. ITP is classified based on duration into newly diagnosed, persistent (3– <12 months), and chronic (≥12 months) [11].

Participants

Patients were excluded from the study if they were classified as newly diagnosed ITP [**Error! Bookmark not defined.**]; or received treatment outside the hospital or patients with thrombocytopenia associated with other systemic disorders (e.g., malignancy, infections, collagen vascular disorders, etc.). The study was approved by the research ethics committee, faculty of medicine, Cairo University (Code: MD-148-2019).

Procedures

Data was extracted from the medical records including patients' demographics (age at diagnosis & gender), clinical characteristics (initial presenting symptoms, bleeding history, grade of bleeding (described below), liver enzymes, and CBC: at presentation, at 1 week, at 1 year from presentation, and finally date of last follow up.

For grading, bleeding manifestations were grouped into three major domains: skin (S), visible mucosa (M), and organs (O), with gradation of severity (SMOG). Each bleeding manifestation is assessed at the time of examination. Severity is graded from 0 to 3 or 4, with grade 5 for any fatal bleeding. Bleeding reported by the patient without medical documentation is graded 1. Within each domain, the same grade is assigned to bleeding manifestations of similar clinical impact. The "worst bleeding manifestation since the last visit" (observation period) is graded, and the highest grade within each

domain is recorded. The SMOG system provides a consistent description of the bleeding phenotype in ITP [12].

Type of treatment at diagnosis and maintenance treatment if needed were recorded.

All patients with persistent and chronic ITP were tested for HCV. First, antibody test (by ELISA): which establishes whether patient has ever been exposed to HCV. Second, PCR test (If ELISA is positive) to detect if the virus is still active and necessitates treatment.

Primary outcome parameters included estimating the prevalence of HCV infection among patients with persistent and chronic ITP, evaluation of platelet counts in HCV-positive patients in comparison to HCV-negative patients and assessing efficacy of different treatment options in HCV-positive persistent and chronic ITP patients.

The criteria for response to the ITP treatments was classified according to International Working Group (IWG) [10]. Complete response (CR) is defined as any platelet count of at least or more than 100 x10^9/L. Response (R) is defined as any platelet count between 30 and 100 x 10^9/L and at least doubling of the baseline count. No response (NR) is defined as any platelet count lower than 30 x 10^9/L or less than doubling of the baseline count. Loss of CR or R means platelet count below 100 × 10^9/L or bleeding (from CR) or below 30 × 10^9/L or less than 2-fold increase of baseline platelet count or bleeding (from R). The response term requires concurrent resolution of bleeding.

Statistical analysis

Data was analyzed using IBM SPSS advanced statistics version 24 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. The student t test was used for comparison of quantitative variables, and the chi-square test or the Fisher exact test were used for comparison of qualitative variables. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

Demographic, clinical, and laboratory data of 87 studied patients are demonstrated in Table 1. The mean duration of disease was 2.6 years ± 2.08 SD with range (1 – 12 years). Grading of bleeding was categorized according to SMOG score; there was organ bleeding in 10 cases (11.5%) in the form of hematuria (4 patients), GIT bleeding (4 patients), menorrhagia (1 patient) and finally ocular bleeding in 1 patient (Table 1).

Table 1 Demonstrating Characteristics of Studied Patient

Characteristic	**Subgroup (Total number = 87 patients)**		**N**	**%**
Gender	● Male		50	57.5%
	● Female		37	42.5%
Age (years)	● At diagnosis	Min -Max	0.5 – 12	
		Mean ± SD	5.95 ± 3.29	
		Median (IQR)	6.0 (3 – 8.25)	
	● At assessment	Min -Max	2.5 – 16	
		Mean ± SD	8.38 ± 3.39	
		Median (IQR)	7 (5.75 – 11.5)	
Initial presentation symptoms	● Skin bleeding		49	56.5%
	● Mucosal bleeding		8	9%

	● Organ bleeding		1	1%
	● Accidentally discovered		4	4.5%
	● Combined bleeding sites (n, 25)	Skin and mucosal	19	29%
		Skin and organ	2	
		Skin, mucosal and organ	4	
Grading of bleeding (SMOG)	● Skin bleeding	S0	13	15%
		S1	4	4.6%
		S2	40	46%
		S3	30	34.4%
	● Mucosal bleeding	M0	56	64.4%
		M1	6	6.9%
		M2	17	19.5%
		M3	8	19.5%
	● Organ bleeding	O0	77	88.5%
		O1	4	4.6%
		O2	6	6.9%
Complete blood picture at initial presentation	● Hemoglobin (gm/dL)	Min -Max	6.9 - 14.2	
		Mean ± SD	11.29 ± 1.59	
		Median (IQR)	11.6 (10.3 - 12.3)	
	● Total leucocyte count (/microliter)	Min -Max	2.3 - 21	
		Mean ± SD	9.2 ± 3.56	
		Median (IQR)	9 (6.5 - 10.5)	
	● Platelets (/microliter)	Min -Max	0 - 65	
		Mean ± SD	35.02 ± 24.34	
		Median (IQR)	24 (15 - 50)	
	● Reticulocyte count (%)	Min -Max	0.2 - 7.1	
		Mean ± SD	2.06 ± 1.22	
		Median (IQR)	1.8 (1.5 - 2.5)	
Initial treatment	● Watch full waiting		4	4.6%
	● Steroid (intravenous or oral)		66	75.9%
	● Intravenou steroid (methylprednisolone) and IVIG		17	19.5%
Maintenance treatment	● Oral Prednisolone		77	88.5%
	● Azathioprine		61	70.1%
	● Eltrombopag		29	33.3%
	● Cyclosporin		14	16.1%
	● Mycophenolate mofetil (MMF)		5	5.7%
Blood products transfusion	● PRBCs and Platelets (n, 6, 60%)	Bleeding per rectum	2	33.3%
		Menorrhagia	1	16.7%
		Epistaxsis	3	50%
	● PRBCs (n, 2, 20%)	Epistaxsis and menorrhagia	1	50%
		Bleeding per rectum & menorrhagia	1	50%
	● Platelets (n, 2, 20%)	Bleeding per rectum & hematuria	1	50%
		Bleeding per rectum & hematuria	1	50%
Comorbidity (n, 15)	● Cytomegalovirus infection		3	20%
	● Epstein–Barr virus infection		1	6.7%
	● Helicobacter pylori		3	20%
	● Hepatitis C virus (positive antibody)		5	33.3%
	● Combined (n, 3, 20%)	HCV & Helicobacter pylori	2	13.3%
		HCV & Hepatitis B virus	1	6.7%
Liver Enzyme Profile	● Normal (n, 78, 89.7%)	HCV antibody negative	72	92.3%
		HCV antibody positive	6	7.7%
	● Elevated (n, 9, 10.3%)	HCV antibody negative	7	77.8%
		HCV antibody positive	2	22.2%

Abbreviations: gm/dL, gram per deciliter; HCV, Hepatitis C virus; IQR, the interquartile range; IVIG, intravenous immunoglobulin; PRBCs, packed red blood cells; SD, standard deviation; SMOG, skin (S), visible mucosa (M), and organs (O), (G) gradation of severity

Most patients didn't require transfusion of blood products (77 patients, 88.5%). Different reasons for transfusion of blood products are summarized in Table 1. Liver enzymes were elevated in nine patients (9/87, 10.3%), and positive HCV antibody was detected in two patients only (2/9, 22.2%), (Table 1). There was statistically significant difference between the initial platelet count and each of platelet count at 12 months of treatment (p=0.003) and at end of study (p<0.001). Similarly, there was statistically significant difference between platelet count at one week and each of platelet count at twelve months of treatment (p=0.037) and platelet count at the end of study (p<0.001). However, no statistically significant difference was found between the initial platelet count and platelet count at one week, or between platelet count at twelve months of treatment and platelet count at the end of study. Data was not available for three patients at one week, 15 patients at 12 months and 24 patients at the last visit (Table 2).

Table 2 Comparison between Platelet counts through the study periods

CBC		**Initial**	**One week**	**Twelve months**	**Last visit**	***p*-value**
Platelets (/microliter)	Number of Patients	87	84	72	63	<0.001
	Mean ±SD	35.02 ± 24.34	48.56 ± 53.68	44.47 ± 32.85	55.76 ± 39.13	
p value for comparing between initial and each other periods			0.360	0.003	<0.001	
p value for comparing between 1 week and 12 months						0.037
p value for comparing between 1 week and last visit						<0.001
p value for comparing between 12 months and last visit						0.154

p value <0.05 is signifcant; SD, Standard deviation.

Eight patients (9%) had positive HCV antibody detected by ELISA, 2 of them had combined HCV and helicobacter pylori (diagnosed by helicobacter pylori antigen in stool), and 1 patient had co-infection with HBV (Table 1). Three other patients were positive for helicobacter pylori antigen in stool, three patients had cytomegalovirus (CMV) infection diagnosed by PCR, and one patient had Epstein–Barr virus (EBV) antibodies detected by ELISA. Specific treatment as Ganciclovir for those with CMV infection and triple therapy for helicobacter pylori was prescribed.

Most of the studied patients (79 patients, 91%) were negative for HCV antibody. PCR test for HCV was done for those patients with positive antibody (8 patients, 9%) and one patient was positive for HCV RNA. This was a female patient, 12 years old, who presented with vaginal bleeding, platelet count was zero and hemoglobin level was 8.8 g/dL. She received blood and platelets. Neither the 1st line of treatment (steroids) nor 2nd line treatment (Azathioprine or Eltrombopag) gave response, her last platelet count was 8 x 10^9/l. Also, elevated liver enzymes occurred during the treatment. Although she received anti HCV treatment in the form sofosbovir for 4 months and HCV PCR became negative, she showed no response, and the last platelet count was 11 x 10^9/l.

Comparison between HCV antibody positive and HCV antibody negative patients showed no statistically significant difference in demographic and clinical data except for co-infection with H Pylori or HBV, where 37.5% of patients with positive HCV antibody have comorbidity compared to 3.8% of patients with negative HCV antibody (p value = 0.02) (Table 3).

Table 3 HCV antibody status in relation to different prognostic factors

		HCV antibody				
Demographic data		**Negative (n = 79)**		**Positive (n = 8)**		**P value**
		No.	**%**	**No.**	**%**	
Sex						
Female		33	41.8	4	50.0	0.718
Male		46	58.2	4	50.0	
Age at diagnosis (years)						
Min. – Max.		0.50 – 12.0		0.50 – 12.0		0.326
Mean ± SD.		6.05 ± 3.24		5.0 ± 3.77		
Median		6.0		4.50		
Age during assessment (years)						
Min. – Max.		2.50 – 16.0		4.0 – 13.50		0.691
Mean ± SD.		8.43 ± 3.38		7.88 ± 3.65		
Median		7.0		7.50		
Duration of disease (years)						
Min. – Max.		1.0 – 12.0		1.0 – 5.50		0.210
Mean ± SD.		2.38 ± 1.89		2.88 ± 1.71		
Median		1.50		2.0		
Initial presentation						
No symptoms		4	5.1	0	0.0	1.000
Cutaneous bleeding		67	84.8	7	87.5	
Mucosal or orifical bleeding		30	38.0	3	37.5	
Organ bleeding		11	13.9	1	12.5	
Grading of bleeding						
S	**S0**	12	15.2	1	12.5	0.302
	S1	3	3.8	1	12.5	
	S2	37	46.8	2	25.0	
	S3	27	34.2	4	50.0	
M	**M0**	51	64.6	5	62.5	0.549
	M1	6	7.6	0	0.0	
	M2	14	17.7	3	37.5	
	M3	8	10.1	0	0.0	
O	**O0**	70	88.6	7	87.5	0.632
	O1	4	5.1	0	0.0	
	O2	5	6.3	1	12.5	
G	**G0**	4	5.1	0	0.0	1.000
	G1	3	3.8	0	0.0	
	G2	26	32.9	3	37.5	
	G3	27	34.2	4	50.0	
	G4	7	8.9	0	0.0	
	G5	10	12.7	1	12.5	
	G6	1	1.3	0	0.0	
	G8	1	1.3	0	0.0	
Need blood products						
No		71	89.9	6	75.0	0.228
Yes		8	10.1	2	25.0	
Type of treatment						
Initial	**Watchful waiting**	4	5.1	0	0.0	1.000
	Steroid (iv or oral)	59	74.7	7	87.5	
	IV Steroid and IVIG	16	20.3	1	12.5	
Maintenance	**Oral prednisone**	72	91.1	5	62.5	0.046
	Azathioprine	54	68.4	7	87.5	0.426
	Eltrombopag	12	15.2	2	25.0	0.610
	Cyclosporin	4	5.1	1	12.5	0.390
	MMF	22	27.8	7	87.5	0.002
Disease status (Response) at different times of assessment						
One week	**Not Assessed**	1	1.3	0	0	0.751
	No Response	51	64.6	6	75	
	Response	27	34.2	2	25	

	Relapse	0	0	0	0	
Twelve months	**Not Assessed**	13	16.5	0	0	0.204
	No Response	25	31.6	4	50	
	Response	40	50.6	3	37.5	
	Relapse	1	1.3	1	12.5	
At last visit	**Not Assessed**	24	30.4	0	0	0.102
	No Response	13	16.5	4	50	
	Response	41	51.9	4	50	
	Relapse	1	1.3	0	0	
Presence of comorbidity						
No		72	91.1	5	62.5	0.027
CMV		3	3.8	0	0	
EBV		1	1.3	0	0	
H Pylori		3	3.8	2	25	
Positive HBV		0	0	1	12.5	

p value <0.05 is significant; SD, Standard deviation; SMOG; skin (S), visible mucosa (M), and organs (O), with (G) gradation of severity

DISCUSSION

Immune thrombocytopenia (ITP) is the most common cause of acquired thrombocytopenia in childhood [13]. Most of patients have mild symptoms but severe and life-threatening bleeding may occur, ITP remains a diagnosis of exclusion. Half of cases recover within the 1st month and 70-80% of cases improve in the first 6-12 months [14]. Forty percent of children with ITP develop persistent ITP and 10–20% goes toward a chronic form of the disease [15].

The data gathered in studies showed an impact of different types of infection on the chronicity of ITP. Viruses like CMV and EBV are considered risk factors in patients with ITP. Wu et al. found a significant correlation between CMV and EBV infections and ITP [16].

Chronic HCV infection has been associated with the development of extrahepatic manifestations including thrombocytopenia. Previous studies reported prevalence of thrombocytopenia in patients with chronic HCV ranging from 0.16% to 45.4% [17]. ITP is associated with high morbidity in HCV–infected patients [18], but the relationship between these diseases is unclear [19]. The relationship between HCV and ITP is a mutual relationship, as HCV infection is a recognized cause of secondary ITP [20]. Patients with HCV-ITP are distinct from those with primary ITP, they have different clinical presentations and pathogenesis [21].

Egypt, a lower middle-income country with a population of 100 million, had one of the highest burdens of HCV infections globally [22]. In 2008, 15% of the population had antibodies to HCV (seropositive), indicating they had been exposed to the virus, and 1 in 10 Egyptians aged 15–59 years had chronic HCV infection [23]. Faced with this major health and economic burden, Egypt established its first national control program for HCV in 2008, focused on expanding access to treatment. In 2014, Egypt issued its second national program for mitigating HCV, with emphasis on prevention, education, and improved patient care for those living with HCV [24].

In the present study, we investigated the association between hepatitis C virus (HCV) infection and persistent or chronic ITP in children. We detected positive HCV antibody tests in 8 patients (9%), PCR HCV confirmed positivity in one patient. We could not identify an association between HCV infection and ITP, this would require testing more patients to deny or prove this association. A positive hepatitis C antibody test does not necessarily mean current infection. In about 25% of patients, acute infection

is followed by viral clearance. This is called 'spontaneous clearance'. Most of these individuals clear infection by 6 months (73–86%) or 12 months (87– 95%) [25]. On the other side, negative PCR results; persons in whom HCV RNA cannot be detected may have recovered from an infection or have levels so low as to be undetectable by even this ultrasensitive assay. Patients with normal serum aminotransferase levels and who are ELISA and recombinant immunoblot assay-positive but PCR-negative most likely have recovered from an HCV infection, although the possibility that they may have an intermittent viremia or a circulating RNA level too low to be detected by PCR cannot be ruled out entirely. They should therefore be advised to have their serum aminotransferase levels checked periodically for up to 12 months; if these remain within the normal range, recovery from HCV infection can be presumed [26].

HCV infection clearance or persistence is affected by a complex set of interactions between virus and host that is only partly understood. Host factors such as female sex [27], initial immune response [28 ,29], virus specific neutralizing antibodies [30], and host genetics [31] have been associated with clearance in prospective studies of acute HCV infection. Pathogen-associated factors, such as diversity of HCV viral quasispecies [32] and HCV genotype [33], might also be linked with viral clearance.

The current study showed that none of these parameters: age, gender, initial presentation symptoms, disease duration, bleeding grade, transfusion of blood products, treatment type and response to treatment; was statistically associated with HCV antibody positivity. Comparison between HCV antibody positive and HCV antibody negative patients showed no statistically significant difference in demographic and clinical data except for co-infection with H Pylori or HBV, where 37.5% of patients with positive HCV antibody have comorbidity (3/8 patients) compared to 11.4% of patients with negative HCV antibody (9/79 patients) (p value = 0.02) (Table 3).

Previous studies reported that the persistence of the underlying infection, for example in HIV, HCV, CMV and Helicobacter Pylori infections is strongly associated with chronicity and severity of ITP [34]. Our data showed that there was no statistical difference, between patients with comorbidity and those without, in relation to response status at the last assessment (p value = 0.3). Contrastingly, Lee et al reported, in a study of 75 patients diagnosed as Helicobacter pylori infection, that the successful eradication of Helicobacter pylori infected ITP patients tended to increase the platelet count. Furthermore, sustained Helicobacter pylori infection, due to a failed eradication attempt, showed poor response to platelet recovery [35]. This finding is similar to a study by Hodeib et al. who conducted the study on one hundred Egyptian children with ITP, he concluded that Helicobacter pylori eradication therapy was effective in increasing platelet count in Helicobacter pylori positive chronic ITP patients [36].

ITP is associated with high morbidity in HCV infected patients [37], but the relationship between these diseases is unclear. HCV infection has been associated with the development of a number of extra hepatic manifestations including thrombocytopenia which is one of the most common hematological abnormalities [38]. Successful eradication of HCV may now be possible in a high proportion of patients given the current ability to treat thrombocytopenic HCV-infected patients with newer, less toxic agents but it remains unclear how often elimination of HCV will result in a substantial increase in basal platelet count in these patients [39].

Hodeib et al conducted a cross-sectional study screening of HCV infection on children aged 3-15 years at Pediatric Departments of the University Faculty of Medicine and the General Hospitals in Beni-Suef during the period from June 2018 through February 2020. He reported that HCV infection is highly prevalent among high-risk children aged 3-15 years. Blood transfusion, IV injection and exposure to surgery are independent risk factors for infection in this population [40]. So blood transfusion may be a risk factor for acquiring HCV infection in patients with ITP who received blood products. However, the current study did not find a statistically significant impact of blood products' transfusion on HCV antibody status (p value = 0.22), as 80% of patients (8/10) who received blood products (blood and/or platelets) were HCV antibody negative.

Only one patient, in this study, was diagnosed with active HCV infection (positive HCV PCR and elevated liver enzymes), and 7 patients had evidence of previous exposure to HCV (positive HCV antibody by ELISA, negative HCV PCR and normal liver enzymes). This could be explained either by recovery from infection or a false positive antibody testing by ELISA. Different results could have been obtained if platelet counts were assessed in a cohort of HCV infected pediatric population. For instance, in one study the incidence rate of ITP among HCV infected individuals was compared to that of matched HCV-uninfected individuals. HCV infection was associated with an elevated risk of developing ITP among both untreated and treated patients [41]. In another study, the platelet count in HCV-positive patients was found to be significantly lower than in HCV-negative patients [42].

The current study has certain limitations by even this ultrasensitive assay. First, HCV status was not checked at the time of diagnosis. Second, although sample size was accepted but only one patient had positive HCV PCR.

In conclusion, this study demonstrates that HCV infection is not a relatively frequent comorbidity among our cohort of pediatric patients with persistent and chronic ITP. Further prospective studies including a large number of patients should be designed for better assessment of HCV status in pediatric patients with persistent and chronic ITP.

Declarations

Ethics approval and consent to participate: This study was performed in line with the principles of the Declaration of Helsinki and its later amendments. The Research Ethics Committee of the Faculty of Medicine, Cairo University, has approved this research under the Code: MD-148-2019. Written informed consent was obtained from the parents.

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