Hepatitis A Encephalopathy Clinical and Laboratory Study Children Welfare Teaching Hospital

Zainab Fadhil Al Khalifa, Dhiaa Hassen Al Beldawi***

ABSTRACT:

BACKGROUND:

Hepatitis A virus is a small spherical non-enveloped virus classified under the family Picornaviridae . It is highly contagious. Transmission is by person to-person contact through the fecal–oral route. Poor sanitation and personal hygiene, and consumption of contaminated food and water, are the commonest causes of HAV transmission. It is a viral liver disease that has a clinical spectrum ranges from asymptomatic infection to fulminant hepatitis and hepatic encephalopathy which is possibly reversible with treatment. The implementation of routine vaccination of children seems, in the long term, the most reasonable way to get recurrent outbreaks under control.

AIM OF THE STUDY:

To evaluate the clinical and laboratory findings in HAV infection in patients with and without encephalopathy.

METHOD:

It was A prospective hospital based study was done from March 2018 to July 2019 carried out in the Children Welfare Teaching Hospital in Baghdad included 59 patients whom admitted, all were diagnosed as acute hepatitis A infection as defined by the presence of anti- hepatitis A immunoglobulin M. The clinical data collected by history taking and clinical examination, biochemical and imaging data collected in questionnaire papers for each patient, then all data gathered in an Excel table and statistical analysis done.

RESULTS:

A total number of 59 patients were admitted to Children Welfare Teaching Hospital diagnosed as hepatitis A infection, included in our study, 27 (45.7%) Male, 8 (29.6 %) of them had encephalopathy, and 32 (54%) were female,11 (34.3%) of them had encephalopathy. the study had showed that the statistically significant factors for hepatic encephalopathy were PTT, INR, bleeding and ascites .

CONCLUSION:

The present study has concluded that the rate of hepatic encephalopathy among patients with hepatitis A infection is relatively high, the abnormality in coagulation profile, the presence of bleeding tendency and ascites were statistically important factors in the development of encephalopathy in patients with hepatitis A infection, most affected children were between 5 and 10 years old, patients living outside of Baghdad had higher rates of encephalopathy.

KEY WORDS: Hepatic encephalopathy, Encephalitis associated with hepatitis A, Severe acute liver failure related to viral hepatitis.

INTRODUCTION:

Hepatitis A virus (HAV) is a small spherical non-enveloped virus classified under the family Picornaviridae, genus Hepatovirus. The viral genome is a single-stranded positive sense RNA[(1)]. It is thermostable and acid resistant. One of the more common causes of acute hepatitis is hepatitis A[(2,3)]. It is an acute, necroinflammatory disease of the liver[1]. Almost everyone recovers fully from hepatitis A with a lifelong immunity. However, a very small proportion of people infected with hepatitis A could die from fulminant hepatitis[(4)].

Clinical Manifestations: The incubation period is 14 to 28 days (up to 50 days)[(5)]. The onset of hepatitis A is characterized by: Prodromal symptoms including anorexia, nausea, malaise, and fever. In children, gastrointestinal symptoms such as diarrhea and vomiting may predominate. Jaundice, dark urine and pale stools follow within a few days. Mild to moderate tender hepatomegaly is often detected. Splenomegaly and posterior cervical lymphadenopathy may occur.

*Baghdad Teaching Hospital, Medical City, Baghdad, Iraq
**Children Teaching Hospital, Medical City, Baghdad, Iraq

Rarely, extra hepatic manifestations such as arthritis and vasculitis may accompany the acute illness. Serum aminotransferase rise rapidly during the prodromal period. Serum bilirubin levels peak later and decline less rapidly than serum aminotransferases. The prothrombin time is usually normal. Persistently abnormal coagulation is an indication for referral to specialist center as it may indicate the development of fulminant hepatitis[1] .

Hepatic Encephalopathy (HE): is an altered level of consciousness as a result of liver failure [(6)] .It can be either acute and reversible, or chronic and progressive leading to coma and death[(7,8)] .

Diagnosis: The two main diagnostic tests for HAV are anti-HAV immunoglobulin M (IgM) and anti-HAV IgG (or total antibody). Anti-HAV IgM peaks during the acute phase of acute hepatitis A and persists for 4–6 months[(1)] .

Prevention: Adequate supplies of safe drinking water and proper disposal of sewage within communities, combined with personal hygiene practices, such as regular hand washing, reduce the spread of HAV[(9)].The implementation of routine vaccination of children and/or adolescents, which has recently proved very effective in its effect on general HAV epidemiology, seems, in the long term, the most reasonable way to get recurrent outbreaks under control.

Treatment: There is no specific treatment for hepatitis A. Supportive treatment consists of intravenous hydration as needed and antipruritic agents, rest, nutritional support, and the use of antiemetics and antipyretics[11]and fat-soluble vitamins for the prolonged cholestatic form of disease. Serial monitoring for signs of fulminant hepatic failure[(12).]

Prognosis: Jaundice persists for less than 2 weeks in the majority of cases. Clinical illness and laboratory abnormalities recover within 2 months from onset of illness. Children almost universally recover from HAV infections[(1)].

PATIENTS AND METHODS:

A prospective cross sectional hospital based study was done from March 2018 to July 2019 carried out in the Children Welfare Teaching Hospital in Baghdad. All patients included in this study were hospitalized during this period when severe gastroenteritis and dehydration, alteration in mental sensorium and abnormal bleeding profile was present and the patients who were not hospitalized were excluded from the study. Our study includes 59 patients aged between 2 to 12 years. Patients included in this study had diagnosed as acute hepatitis A infection as defined by the presence of anti- hepatitis A immunoglobulin M.

The clinical data collected by history taking and clinical examination, biochemical and imaging data were collected from the patients at time of presentation to hospital and admission for appropriate management. And the patients whom developed encephalopathy investigations at time of developing encephalopathy had taken and included in the study. The questionnaire included the following data:

1. Demographic characteristics: age, gender and residency.
2. Clinical Manifestations: duration of jaundice, bleeding, ascites, splenomegaly and level of consciousness
3. Laboratory tests: serum ammonia, serum zinc, serum lactate dehydrogenase, liver enzymes, serum bilirubin, coagulation profile, serum albumin, renal function test, complete blood cell and abdominal ultrasound findings.

Encephalopathy stage had clinically assessed and patients were also assessed by a paediatric neurologist . Then were classified according to Nelson textbook criteria:

Table 1: Stages of hepatic encephalopathy [12].

Stages				
	I.	II.	III.	IV.
Symptoms	Periods of lethargy; euphoria; reversal of day night sleeping; may be alert	Drowsiness; inappropriate behavior; agitation; wide mood swings; disorientation	Stuper but arousable; confused; incoherent speech	Coma; a response to noxious stimuli; b no response
Signs	Trouble drawing figures; performing mental tasks	Asterixis; fetor hepaticus; incontinence	Asterixis; hyperreflexia; extensor reflexes; rigidity	Areflexia; no asterixis; flaccidity;
Electroence phalogram	Normal	Generalized slowing;q waves	Markedly abnormal; triphasic waves	Marktedly abnormal; bilateral slowing; d waves; electric-cortical silence

In this study, we analyzed the risk factors for morbidity and mortality. Statistical analysis of the results was made by applying the chi- squared test of significance and students t-test at 0.05 level.

RESULTS:

A total number of 59 patients were admitted to Children Welfare Teaching Hospital diagnosed as hepatitis A infection, included in our study, table 2 shows that The residence of the patients included in our study divided into: Baghdad center 33, 9 of them had encephalopathy. Baghdad periphery 10, 1 of them had encephalopathy, other (outside of Baghdad) 16, 9 of them had encephalopathy. This is statistically significant and the p value is 0.032.

Table 2: Demographic characteristics of studied patients.

		Encephalopathy		No		P value
		No.	%	No.	%	
Gender	Male	8	42	19	47.5	0.698
	Female	11	58	21	52.5	
Age (years)	<5y	8	42	12	30.0	0.654
	5---9	8	42	20	50.0	
	10_12y	3	16	8	20.0	
	Mean±SD (Range)	6.3±3 (2.5-12)		6.8±3 (2-12)		
1Residence	Baghdad-center	9	47.4	24	60.0	0.032*
	Baghdad-periphery	1	5.3	9	22.5	
	Other	9	47.4	7	17.5	

*Significant difference between proportions using Pearson Chi-square test at 0.05 level.

Table 3 Shows that 2 patients died (10.5%) of patients with encephalopathy, both were female and aged 4 years.

Table 3: The difference in the incidence of grades of hepatic encephalopathy.

		Encephalopathy	
		No	%
Grade of encephalopathy	Grade I	4	21
	Grade II	3	16
	Grade III	7	37
	Grade Iva	2	10.5
	Grade IVb	3	16
Outcome	Dead	2	10.5
	Alive	17	89.5

Table 4 shows the difference in the incidence of duration jaundice before the development of hepatic encephalopathy in days. The mean duration of jaundice before the development of hepatic encephalopathy was 4.8 days.

Table 4: Incidence of jaundice duration before development of encephalopathy.

		Encephalopathy	
		No.	%
Duration between jaundice and encephalopathy (days)	1 day	1	5
	2	3	15
	3	2	10.5
	4	2	10.5
	5	2	10.5
	6	3	16
	7	5	26
	8 days	1	5
	Mean = 4.8 days		

Table 5 shows the difference in mean of the liver function tests between the two study groups. The mean of partial thromboplastin time in patients with encephalopathy was 44+_21(21.5-120), while it was 35+_8(22-62) in patients without encephalopathy which is statistically significant and the p value is 0.021 .The mean of INR in patients with encephalopathy was 2.5+_2 (0.8-11), while it was 1+_0.8(0.7-5) in patients without encephalopathy. This difference is statistically significant and the p value is 0.008.

Table 5 : Difference in the mean of liver function tests between the two study groups .

	Encephalopathy	No	P value
ALP	392±244 (105-1003)	463±357 (197-1896)	0.433
ALT	976±727 (240-2659)	920±1062 (125-4495)	0.836
AST	721±635 (103-2208)	571±615 (85-2501)	0.391
TSB	15±10 (2.5-42.6)	10±8 (1.2-40)	0.059
Direct	10±7 (2-33)	7±6 (1-30)	0.086
PT	25±19 (10-70)	17±12 (10-72)	0.056
PTT	44±21 (21.5-120)	35±8 (22-62)	0.021*
INR	2.5±2 (0.8-11)	1± 0.8 (0.7-5)	0.008*

-Data were presented as Mean±SD (Range)
*Significant difference between two independent means using Students-t-test at 0.05 level.

Table 6: The difference in mean of serum ammonia, serum zinc and serum LDH in the two study groups.

	Encephalopathy	No	P value
Serum ammonia	118±80 (16-280)	71±60 (15-269)	0.108
Serum Zinc	67±6 (55-85)	66±6 (54-80)	0.702
LDH	402±253 (246-1412)	389±161 (242-1118)	0.816
-Data were presented as Mean±SD (Range)			

*Significant difference between two independent means using Students-t-test at 0.05 level.

Table 7: The difference in mean of blood cells count and renal indices in the two study groups.

	Encephalopathy	No	P value
Haemoglobin	11±1.2 (9-13)	11±1.7 (6-14.6)	0.334
WBC	10.8±6.6 (4.6-28.4)	9.3±3.4 (4.1-21)	0.230
Platelets	337±152 (56-653)	368±134 (107-703)	0.429
Blood urea	18±8 (9-41)	23±9 (8-40)	0.064
Serum creatinine	0.4±0.15 (0.2-0.6)	0.4±0.2(0.2-1)	0.539
-Data were presented as Mean±SD (Range)			

*Significant difference between two independent means using Students-t-test at 0.05 level.

Table 8 shows the incidence of encephalopathy among our studied patients in regards to the presence or absence of abdominal ultrasound findings and some clinical signs and symptoms. Ascites (Abdominal distention) was found in 12 (63%) of patients with encephalopathy and in 7(17.5%) in patients without encephalopathy, while it was absent in 7(37%) of patients with encephalopathy and in 33(82.5%) in patients without encephalopathy.

This difference is statistically significant and the P value is 0.0001 . Bleeding (melena, hematemesis and epistaxis) was found in 8 (42%) of patients with encephalopathy and in 7(17.5%) of patients without encephalopathy, while it was absent in 11(57%) of patients with encephalopathy and in 33(82.5%) of patients without encephalopathy. This difference is statistically significant and the P value is 0.043.

Table 8: The presence or absence of the clinical Manifestations and ultrasound findings in the two study groups.

		Encephalopathy		No		P value
		No.	%	No.	%	
Porta hepatis LAP/hepatitis: u/s	Yes	3	16	7	17.5	0.870
	No	16	84	33	82.5	
Thick/edematou.s wall of GB :u/s	Yes	6	31.6	10	25	0.595
	No	13	68.4	30	75	
Splenomegaly	Yes	4	21	13	32.5	0.364
	No	15	79	27	67.5	
	No	5	26	15	37.5	
ascites	Yes	12	63	7	17.5	0.0001*
	No	7	37	33	82.5	
Bleeding (H/M/Epistaxis)	Yes	8	42	7	17.5	0.043*
	No	11	58	33	82.5	

*Significant difference between proportions using Pearson Chi-square test at 0.05 level.

Analysis of data was carried out using the available statistical package of SPSS-25 (Statistical Packages for Social Sciences- version 25). Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values).

The significance of difference of different means (quantitative data) were tested using Students-t-test for difference between two independent means. The significance of difference of different percentages (qualitative data) was tested using Pearson Chi-square test (χ^2-test) with application of Yate's correction or Fisher Exact test whenever applicable.

Statistical significance was considered whenever the P value was equal or less than 0.05[13,14]

DISCUSSION:

In the present study there were 27(46%) Male and 36 (54%) female ,Male –to- female ratio 1:1.3.while a- study in China showed the incidence rate of hepatitis A cases were higher in males than in females[15]. The slightly higher female ratio in the current study may be incidental due to small sample size.

The mean age of the patients in this study is 6.5 years with a range of 2 -12 years .Of these patients, 48/59 (81%) were below 10 years and 20/59 (34 %) were below 5 years; so, most

patients were between 5 and 10 years . While a Pakistani study showed that the mean age of patients in the study was 5.3 years with a range 1.8-11 years. Of these patients, 27/30 (96.7%) were below 10 years and 18/30 (60%) below 5 years; so, most patients were below 5 years[16] . This may be because that the children have more contact with other children and more outside eating at school age in our society and in other countries younger children have more day care contact with others .The present study shows that the incidence of hepatic encephalopathy among the study group was 32%**,** which was relatively high because the current study involves the inpatients only and had excluded the outpatients, hepatic encephalopathy is a rare complication as mentioned in the textbook of diseases of the liver and biliary system in children[2]. Of these cases the majority, 37% were in grade 3 encephalopathy, 26% were in grade 4, 21% had signs of grade 1 encephalopathy, 16% were in grade 2. The mean interval between the onset of jaundice and the presence of clinical encephalopathy was 4.8 days. While in the Pakistani study, the majority of patients with encephalopathy were in grade 4, 48%, 24% were in grade 2, 16.7 % had signs of grade 1 encephalopathy, and the mean interval between the onset of jaundice and the presence of clinical encephalopathy was 13.5 days [16]. This was may be an incidental results in both the Pakistan and the present study and may be modified with different groups' sizes.

In regards to liver function test, aspartate aminotransferase results in this study were higher in patients with encephalopathy but statistically not significant regarding developing hepatic encephalopathy (p = 0.086), Also both ALT (P 0.816) and LDH (P 0.836) were higher in patients with encephalopathy but statistically not significant.While in other study in Iran[17], AST was (p 0.045), which was statistically significant, and in other study in Korea , alanine aminotransferase (ALT) (P<0.001), lactate dehydrogenase (LDH) (P = 0.045) were statistically significant regarding influencing the severity of hepatitis A and hepatic encephalopathy. The total and direct bilirubin results in the current study were higher in patients with encephalopathy (mean =15+_10, 10+_7 resp.) than in patients without encephalopathy (mean = 10+_8 , 7+_6 resp.) but the results also were statistically not significant (p = 0.059 , 0.086 resp.), while the bilirubin results in the study in Iran were statistically significant in comparison between patients with and without encephalopathy p= (0.031) [17]. The higher mean of these parameters in hepatic encephalopathy in the present study is due to more severe hepatocellular damage in cases of encephalopathy may become statistically significant with larger study group.

The present study showed statistical significance of partial thromboplastin time, international normalized ratio in regards to developing hepatic encephalopathy (p value was 0.021, 0.008 respectively). Also, other study in Iran[17] showed same statistical results regarding partial thromboplastin time and international normalized ratio and development of encephalopathy (p = 0.04, 0.009 respectively). Acute and chronic liver diseases impair coagulation factors synthesis.

In this study, the prothrombin time was higher in patients with encephalopathy (mean = 25+_19) than in patients without encephalopathy (mean = 17+_12), but statistically not significant (p = 0.056) . While in the Pakistani study, there was correlation between prothrombin time and grade of encephalopathy (P <.01). In this study, both of 2 cases died had prolonged prothrombin time. (>70 and 32). One of them had bleeding and given blood transfusion. This agrees with the results of the Pakistani study where prothrombin time was the most significant predictor of survival (P < .02)[(16)]. This is due to more severe liver damage, so it is of important prognostic value as mentioned in many textbooks.

Regarding serum ammonia, it was higher in patients with encephalopathy (mean =118.8) than in patients without encephalopathy (mean =71+_6), but the results were statistically not significant in the present study. The p value was 0.108. Also it was higher in other Pakistani study in patients with high-grade HE, that is, grades 3 and 4 (mean= 51.98+-8 ,76.28+-10.7 resp.), than in the patients with low-grade HE, that is, grades 1 and 2 (mean= 35.17+_4.7 , 37.6+_4.2 resp.). Patients with no evidence of HE had the lowest levels of blood ammonia (mean =29.9+_3.3)[19]. The non-significance in the present study may belong to the fact that some patients were admitted to other hospitals prior to admission to Children Welfare Teaching Hospital and received supportive treatment there that influenced the lab results when admitted to our hospital. Several studies have shown a correlation of serum ammonia with complications related to liver failure such as

cerebral herniation, hepatic encephalopathy, and prevalence of Porto systemic collaterals, that is due to the fact that vast amounts of ammonia escape hepatic metabolism in liver failure leading to high ammonia concentrations in blood, which in turn is associated with increased cerebral ammonia uptake and cerebral herniation. Serum zinc in this study was statistically not significant regarding its level in patients with (mean = 67+-6) and without encephalopathy (m+fean = 66 +-6) (p value 0.702). While in a study at India, there was statistically significant association between low serum zinc level and grades of hepatic encephalopathy (p-value 0.001). Serum zinc mean was low in both patients` groups, so we need more studies regarding serum zinc level in our country. Zinc is an important co-factor for many enzymes. Zn has key role in physiological detoxification of ammonia via urea cycle in liver and as a co factor in ornithine Transcarbamylase (OTC); so, low zinc level associated with decreased OTC activity and higher plasma concentration of ammonia. Low plasma Zn impairs nitrogen cycle in muscle and increase glutamine in blood. As a result in advanced grade in HE there is significantly more drop in plasma Zinc.

Platelet count results are not correlated with the risk of developing hepatic encephalopathy (p= 0.42) in this study, this may be due to small sample size, while other study in Iran low platelet count was statistically significant in regards to the hepatic encephalopathy (p = 0.013)[17]. In this study, the results of renal function were not significant, there was only one case had creatinine 1.02 and didn't have encephalopathy and blood urea was > 35 in 6 cases (up to 41), 2 (10%) of them had encephalopathy. renal dysfunction and increased serum creatinine found in 16.5% of patients in the Pakistani study [16], that may be due to the intravenous hydration and medical treatment given to the patients.

Abdominal ultrasound findings in this study patients was gall bladder wall thickening found in 27% of total patients (31.6% of patients with encephalopathy and in 25% of patients without encephalopathy) (p value0.595). Porta hepatis LAP found in 17% of patients (15.8% of patients with encephalopathy and in 17.5% of patients without encephalopathy) (p value 0.870) .In contrast to other Indian study, Gall bladder (GB) wall thickening was seen in (75.8%) of cases with encephalopathy ($P < 0.01$). Porta nodes were seen in (60%) of cases with encephalopathy ($P < 0.01$) showing that both where statistically significant [21]. That may belong to the personal radiologist experience and to the individual ultrasound devices.

In regards to gastrointestinal bleeding, it was statistically significant in cases of hepatic encephalopathy (p value was 0.043), this agrees with the study in Iran where gastrointestinal bleeding was statistically significant for hepatic encephalopathy (p 0.001)[17]. This is may be because bleeding causes extra burden on the body organs especially the brain because of hypovolemia . Ascites may exceptionally accompany hepatitis A infection in children. Its appearance, however, does not indicate an unfavorable outcome[22] this disagrees with this study statistical results where the difference in the incidence of ascites among patients with and without encephalopathy was statistically significant (p 0.0001). That indicates ascites caused by liver dysfunction and hypalbuminemia causes coinfections and electrolytes disturbance that precipitate encephalopathy.

Splenomegaly was found in 53.5% of total patients included in our study and there was no significance between patients with encephalopathy (21%) and patients without encephalopathy (32.5%), this result is nearly similar to Pakistani study where splenomegaly was found in 16.7% of patients whom developed encephalopathy[16]. Splenomegaly resulted in the advanced period of the liver disease so it is generally rare in acute liver.

CONCLUSION:

The rate of hepatic encephalopathy among patients with hepatitis A infection is relatively high in the present study.

1. The present study has concluded that the abnormality in bleeding profile, the presence of bleeding tendency and ascites were statistically important factors in the development of encephalopathy in patients with hepatitis A infection.
2. The age of hepatitis A infection in most children is between 5 to 10 years due to high contact rate with others in school age.
3. There is higher rate of hepatic encephalopathy among patients living outside of Baghdad, that may be due to the delay in admission to the tertiary hospital and receiving the appropriate management.

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