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Full Length Research Paper

Factors predicting fulminant course of acute Hepatitis A with special emphasis on predictors of mortality in Egyptian children

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Hepatitis A virus (HAV), a non enveloped RNA virus, is particularly resistant and contagious. The infection is spread chiefly by fecal- oral transmission and is a public health problem throughout the world. The main complication of HAV infection is fulminant hepatitis (FH). This study was done on 80 children, 50 with acute hepatitis A virus and 30 developed fulminant hepatic failure, 52 males and 28 females. In fulminant group 12 recovered with normal liver function, but 18 were died. Children recovered from fulminant liver failure had encephalopathy grade 1 or 2. The study showed statistically significant differences between acute hepatitis A virus and low socioeconomic level and bad hygiene (P < 0.004), children received anti convulsive therapy P < 0.009 and also with diabetic children P < 0.004. Total bilirubin > 9.56, Direct bilirubin > 5.11, ALT > 1365.7, AST > 1635.78, Prothrombin time prolonged more than 25.87 seconds are indices for increasing the risk for developing fulminant hepatic failure in children with acute HAV(P <0.000001, P <0.00001, P < 0.00001, P < 0.0001, P <0.00001 respectively). Mortallity rates was statistically significant related to prolonged prothrombin time, decreased ALT and AST, elevation of serum bilirubin and blood urea and serum creatinine and also with high grade of coma (grade 3 and 4). *This study emphasize that* early prediction of FHF can be predicted by simple tests and appropriate medical treatment could block further liver destruction and prevent development of FHF.

Keywords: Hepatitis A virus; fulminant hepatitis; fecal- oral transmission; Risk factors; low socioeconomic level

INTRODUCTION

Hepatitis A virus (HAV), a non enveloped RNA virus, is particularly resistant and contagious. The infection is spread chiefly by fecal- oral transmission and is a public health problem throughout the world. The main complication of HAV infection is fulminant hepatitis (FH) i.e., acute liver failure with encephalopathy, which occurs in less than 1% of cases *(Lemon and Shapiro, 1944).*

In children, hepatitis A virus is considered to be a mild or even in apparent disease in most instances and the proportion of symptomatic infections increases with age *(Stuart et al., 1992).*

However the overall mortality rate from acute hepatitis A is estimated at 0.2% to 0.4% of symptomatic cases and

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age specific rates indicates that mortality is higher in patients 50 years of age and older and in those younger than 5 years of age. Moreover, fulminant liver failure, which accounts for approximately 11% to 13% of liver transplantation performed in children in the United States, is related to HAV infection in approximately 10% of the cases *(Hoofnagle et al., 1995).*

PATIENT AND METHODS

This study was conducted on children patients from different governorates in Egypt treated in outpatient and inpatient clinic of Pediatric Hepatology Department - National Liver Institute (NLI) as a referral center to highlight the current risk factors of hepatitis "A" infection with special emphasis on fulminant hepatitis "A" risk factors and its prognosis. Eighty children (50 with acute hepatitis A virus and 30 with fulminant hepatitis as defined before).

Diagnosis of hepatitis A was established by detection of immunoglobulin M anti HAV antibodies in the serum samples of all children; no children had evidence of pre-existing liver disease (Detected by enzyme linked immunosorbant assay technique (ELISA).

Principle: Kits from Dia Sorin Co.

Careful medical history including nutritional status, drugs, socioeconomic state and history of chronic diseases, also Through clinical examination, Complete blood count (CBC), liver function tests including ALT,AST, Total bilirubin, direct bilirubin, prothrombin time and concentration, serum albumin, alkaline phosphatase, gamma glutamyl transpeptidase, kidney function tests including urea and creatinine and blood sugar were performed in addition to the routine investigations for the care of FHF patients.

Infection with other viruses (hepatitis B virus, hepatitis C virus, Epstein Barr virus, cytomegalovirus) and also autoimmune hepatitis and Wilson's disease were excluded.

Doppler ultrasound on the portal vein and hepatic artery was performed

Signs of liver failure, defined as summation of clinical and biochemical parameters as follow

1- The acute onset of liver disease with no known evidence of chronic liver disease.

2- Biochemical and / or clinical evidence of severe liver dysfunction: hepatic based coagulopathy (PT ≥ 20 seconds or INR ≥ 2.0 that is not corrected by parenteral vitamin K and or hepatic encephalopathy(must be present if PT is 15 – 19.9 seconds or INR is 1.5 – 1.9 but not if the PT is ≥ 20 or INR ≥ 2.0. this definition of acute liver failure by the Pediatric acute liver failure (PALF) study group

All children who developed encephalopathy were treated in the pediatric intensive care unit – National liver institute. The standard classification of encephalopathy was adapted to children according to the following grades of severity; grade 1: child is confused and has mood changes; grade 2: child is drowsy and displays inappropriate behavior ; grade 3: child is stuporous but obeys simple commands; grade 4a: child is comatose but arousal by painful stimuli or 4b: child is in deep coma and does not respond to any stimuli.

Ethical points

During the interview, the respondent of the children was simply informed about the aims of this study and the fact that it is done to improve the health status of all population. Written consent was taken from the respondent who accompanied the child during attending the mentioned hospitals before participating in the research.

Sample size

80 children (50 with acute hepatitis A virus and 30 with fulminant hepatitis) were recruited based on the following assumptions: α=0.05, probability of exposure in controls=91.0%, power=80.0%, ratio of cases to controls=1:1, and Odds ratio of exposure in hepatitis A cases relative to controls=29.0%. The required sample size was determined using PS (power and sample size calculation) software.

Statistical analysis

Statistical analyses were performed using SPSS (SPSS, Inc., Chicago, Illinois), Epi Info (CDC, Atlanta, Georgia), and Log Xact (Cytel Software Corporation, Cambridge, Massachusetts). Differences between hepatitis A and fulminant hepatitis A regarding dichotomous variables were assessed with the chi-square statistic. Chi-square for linear trend was used for associations between categorical variables and hepatitis A status. When the expected number in any cell was less than five, a two-tailed Fisher's exact test was used. Odds ratio (OR) was used to calculate the risk of exposure to these risk factors long with 95 % confidence interval and both were done to measure the strength of association. When comparing two-sample means, Student's t – test was used for normally distributed variables.

Table 1. Study risk factors of fulminant hepatitis infection

Studied variables	Groups: Fulminant hepatitis (F.H.) No	%	Hepatitis "A" cases (H.A) No	%	P- value	Odds ratio	Confidence interval (C.I.)
Age of the child:							
- < 1 year : 5 years	20	66.7	36	72.0	**0.61**	**0.78**	**0.26 – 2.31**
- 5 years : > 10 years	10	33.3	14	28.0			
Sex of the child:							
- Male	22	73.3	30	60.0	**0.23**	**0.55**	**0.18– 1.62**
- Female	8	26.7	20	40.0			
Socioeconomic level:							
- low	25	83.3	27	54.0	**0.008***	**4.26**	**1.27 – 15.15**
- Moderate and high	5	16.7	23	46.0			
Personal hygiene:							
- Bad hygiene	28	93.3	12	24.0	**0.05***	**44.3**	**8.27– 316.6**
- Good hygiene	2	6.7	38	76.0			
Present history of infantile diabetes:							
- Yes	10	33.3	4	8.0	**0.004***	**5.75**	**1.42 – 25.12**
- No	20	66.7	46	92.0			
History of diuretics intake:							
- Yes	6	20.0	1	2.0	**0.01***	**12.25**	**1.3 – 285.75**
- No	24	80.0	49	98.0			
History of anti convulsants:							
- Yes	11	36.7	6	12.0	**0.009***	**4.25**	**1.21 – 15.38**
- No	19	63.3	44	88.0			

Table 2. Mean and one standard deviation of studied variables of hepatitis "A" cases (a cutoff point) as an index for risk of developing fulminant hepatitis

Studied variables	Groups: Fulminant hepatitis (F.H.) No	%	Hepatitis "A" cases (H.A) No	%	Range (F.H.) (H.A)	Mean ± SD (F.H.) (H.A)	P - value	Odds ratio	Confidence Interval (C.I.)
• **Total bilirubin:**									
- ≥ 10.26	28	93.3	13	26.0	9.1 – 28.64	19.9 ± 4.6	**0.000001**	**39.85**	**7.5 – 281.92**
- < 10.26	2	6.7	37	74.0	0.6 - 14.2	7.17±2.39	*		
• **Direct bilirubin:**									
- ≥ 6.21	27	90.0	8	16.0	4.6 – 19.64	12.7± 4.22	**0.00001***	**47.25**	**10.04–259.5**
- < 6.21	3	10.0	42	84.0	0.15 – 8.2	3.89±1.22			
• **AST:**									
- ≥ 1635.78	24	80.0	7	14.0	406 – 1450	1817.5 ± 225	**0.0001***	**24.57**	**6.5 – 100.82**
- < 1635.78	6	20.0	43	86.0	18.1 - 740	1478 ±157.8			
• **ALT:**									
- ≥ 1365.78	26	86.7	6	12.0	332.3 – 1988	1832±276.6	**0.00001***	**47.67**	**10.6 -244.3**
- < 1365.78	4	13.3	44	88.0	116.2 – 667.3	1274.28±91.5			

RESULTS

Among 80 children, 50 with acute hepatitis A virus and 30 developed fulminant hepatic failure, 52 males and 28 females. Only 31 were on breast feeding and 49 were on artificial feeding when infants. Children lived in bad hygiene were 40, other lived in good hygiene were also 40. Those lived in low socioeconomic level were 52 and the other 28 lived in moderate or high socioeconomic level. Diabetes mellitus was found in 14 children and 17 children under anti-convulsive therapy. In fulminant group 12 recovered with normal liver function but 18 were died. Children recovered from fulminant liver failure had encephalopathy grade 1 or 2.

Anicteric hepatitis was founded in 12 children with acute hepatitis group, presented with abdominal pain, fatigability, loss of appetite and hepatomegaly, confirmed by positive Anti HAV IgM and elevated ALT and AST. The other 68 presented with icteric hepatitis and hepatomegaly and only 15 with splenomegaly. In

Table 3. Mean and one standard deviation of studied variables of hepatitis "A" cases (a cutoff point) as an index for risk of developing fulminant hepatitis

Studied variables	Groups: Fulminant hepatitis (F.H.) No	%	Hepatitis "A" cases (H.A) No	%	Range (F.H.) (H.A.)	Mean ± SD (F.H.) (H.A.)	P-value	Odds ratio	Confidence Interval (C.I.)
• **Prothrombin time:**									
- ≥ 27.32 sec	27	90.0	8	16.0	13-79.6	51.53±18.17	**0.00001***	**47.25**	**10.04–259.5**
- < 27.32 sec	3	10.0	42	84.0	12-45	18.57 ± 7.3			
Prothrombn conc. : -									
- < 56.14 %	28	93.3	9	18.0	12.35-98	23.67± 8	**0.0001***	**63.78**	**11.4 – 475.2**
- > 56.14 %	2	6.7	41	82.0	24- 100	63.6± 22.9			
• **Blood sugar (R.B.S.>176 mg/dl)**									
- Positive	10	33.3	4	8.0			**0.004***	**5.75**	**1.42 – 25.12**
- Negative	20	66.7	46	92.0					

Table 4. Mean and one standard deviation of hepatitis "A" cases (a cutoff point) as an index for risk of developing fulminant hepatitis

Studied variables	Groups: Fulminant hepatitis (F.H.) No	%	Hepatitis "A" cases (H.A) No	%	*Range* (F.H.) (H.A)	Mean ± SD (F.H.) (H.A)	P-value	Odds ratio	Confidence Interval (C.I.)
• **Portal vein diameter:**									
- ≤ 6.97	9	60.0	4	26.7	4.1 – 8.4	6.4 ±1.28	**0.049***	**4.13**	**1.01 – 26.5**
- > 6.97	6	40.0	11	73.3	6.5 – 8.6	7.39 ± 0.72			
• **Hepatic artery resistive index:**									
- ≤ 0.64	11	73.3	3	20.0	0.58- 0.66	0.62 ± 0.02	**0.001***	**11**	**1.57 – 93.55**
- > 0.64	4	26.7	12	80.0	0.62– 0.76	0.68 ± 0.05			

Table 5. Study risk factors for mortality of fulminant hepatitis "A" cases

Studied variables	Fulminant Hepatitis Died (18) No	%	Survived (12) No	%	P-value	Odds ratio (O.R.)	Confidence interval (C.I.)
➢ **Encephalopathy grade:**	16	88.9	1	8.3	**0.0000046***	**102**	**6.48 – 4027**
- Grade III and IV	2	11.1	11	91.7			
- Grade I and II							
➢ **Ascitis:**							
- Present	17	94.4	2	16.7	**0.000022***	**85**	**5.28 – 3402.79**
- Absent	1	5.6	10	83.3			

fulminant group only 2 were anicteric and hepatomegaly were founded in 15 (all of the recovered) plus 3 of the died but the remaining who died had not hepatomegaly. Ascites was founded in only 2 with acute hepatitis and founded in 15 of the fulminant group.

In acute hepatitis group 79 returned to normal liver function in a period ranging from 28 – 100 days and only one developed autoimmune hepatitis several months later. Non of the acute hepatitis group and those who recovered from fulminant hepatic failure showed any changes of the kidney function but all of the children died from fulminant hepatic failure showed impaired kidney function during the course of management.

The study showed statistically significant differences between acute hepatitis A virus and low socioeconomic level and bad hygiene ($P < 0.004$), There was statistically significant differences regarding the development of fulminant hepatic failure and previous factors (socioeconomic level) ($P < 0.008$) and bad hygiene ($P < 0.05$).

Table 6. Liver functions as predictors of mortality in fulminant hepatitis "A" cases

Studied variables	Fulminant Hepatitis Died (18) No	%	Survived (12) No	%	Range (F.H.) (H.A)	Mean ± SD (F.H.) (H.A)	P - value	Odds ratio	Confidence Interval (C.I.)
• **Total bilirubin:**									
- ≥ 37.54	14	77.8	1	8.3	29.7 – 98.6	49.9 ± 24.3	**0.00019***	**38.5**	**3.12 – 1097.44**
- < 37.54	4	22.2	11	91.7	16.3 – 26.9	27.24 ± 9.64			
• **Direct bilirubin:**									
- ≥ 13.87	17	94.4	4	33.3	14.6 – 19.64	12.7 ± 4.22	**0.00064***	**34**	**2.68 – 986.08**
- < 13.87	1	5.6	8	66.7	2.4 – 10.2	3.89 ± 1.22			
• **AST:**									
- ≥ 3239.43	16	88.9	2	16.7	1406 – 4450	1817.5 ± 4225	**0.00012***	**40**	**3.67 – 743.62**
- < 3239.43	2	11.1	10	83.3	818.1 – 1740	678 ±1157.8			
• **ALT:**									
- ≥ 2968.42	15	83.3	3	25.0	332.3 – 1988	1832 ± 4276.6	**0.0024***	**15**	**1.92 – 151.57**
- < 2968.42	3	16.7	9	75.0	116.2 – 667.3	674.3 ± 1291.5			
• **Prothrombin time:**									
- ≥ 34.82 sec	17	94.4	1	8.3	33 – 79.6	51.53 ± 18.17	**0.0000025***	**187**	**7.98 – 27136.53**
- < 34.82 sec	1	5.6	11	91.7	22 – 45	18.57 ± 7.3			
• **Prothrombn conc.:**									
- < 30.72 %	16	88.9	1	8.3	12.35 – 98	23.67 ± 8.1	**0.000013***	**88**	**5.5 – 3507.44**
- > 30.72 %	2	11.1	11	91.7	24 – 100	63.6 ± 22.9			

The study showed statistically significant differences between development of fulminant hepatic failure and children received anti convulsive therapy P < 0.009 and also with diabetic children P < 0.004

Total bilirubin > 10.26, Direct bilirubin > 6.21, ALT > 1365.7, AST > 1635.78, Prothrombin time prolonged more than 27.32 seconds are indexes for increasing the risk for developing fulminant hepatic failure in children with acute HAV(P <0.000001, P <0.00001, P < 0.00001, P < 0.0001, P <0.00001 respectively). Also, Portal vein diameter < 6.97 and Hepatic artery resistive index < 0.64 are indexes for development of fulminant hepatic failure in children with acute HAV.

DISCUSSION

This study was undertaken to characterize the factors predicting fulminant course of acute HAV and the predictors of mortality in fulminant HAV in children from Egypt where hepatitis A is the common cause of acute hepatitis in children and can produces significant morbidity.

In this study, only 12 children had anicteric hepatitis, this may be due to that anicteric cases passed unnoticed.

This study showed statistically significant differences between acute hepatitis A virus and low socioeconomic level and bad hygiene, this finding in agreement with most studies and also with *I. I. Salama et al., 2007* who demonstrated that seropositivity to anti HAV antibodies was significantly higher among children with low or very low socioeconomic standard

Bilirubin level > 10.26 was associated with developing fulminant hepatic failure in children with acute HAV in our study, this in agreement with *Makoto Y et al., 2002* also found high serum bilirubin is a predictive of the development of FHF in acute viral hepatitis, but in difference with *Guilhermo R et al., 2003* who found high bilirubin level were independently associated with both low factor V levels and fulminant hepatitis and also with death or transplantation, this difference may be due to the different age between the two studies.

Also, higher bilirubin level was statistically significant related to patients died from fulminant HAV, this in agreement with *Sema A et al., 2005* who founded total and indirect bilirubin levels were found to be significantly higher in patients who died from fulminant hepatic failure in Turkish children,

This study showed that prothrombin time > 27.32 seconds was associated with increased risk of developing fulminant hepatic failure in children with acute HAV and also prolonged prothrombin time when associated with decreased ALT and AST, elevation of serum bilirubin, blood urea, serum creatinine and high grade of coma were associated with high mortality, Similar data was reported by *Uzma S. et al., 2000* who reported that, the prothrombin time was the most

significant predictor of survival. They reported a significant difference between those who survived and those who died on discriminate analysis with respect to age, grade of hepatic encephalopathy, duration of hospitalization, prothrombin time, and duration of jaundice.

The study showed statistically significant differences between development of fulminant hepatic failure and children received anti convulsive therapy this may be due the combined effect of HAV and the hepatotoxic effect of anticonvulsant.

Diabetic children when infected with HAV are at risk of develop FHF, *Vesely et al., 1999*, studied case with hepatitis A that case illustrates that hepatitis A infection may be severe with liver failure, acute renal failure, and permanent diabetes mellitus as a sequel of this infection.

Portal vein diameter < 6.97 and Hepatic artery resistive index < 0.64 are indexes for development of fulminant hepatic failure in children with acute HAV in our study, *Tanaka K et al., 2004* found that The mean resistive index of the hepatic arteries in patients who developed fulminant hepatic failure was significantly larger than that of patients who recovered without developing fulminant hepatic failure ($P < 0.01$). When a resistive index cutoff level of 0.74 was used, an 84% sensitivity and a 94% specificity were obtained for the prediction of fulminant hepatic failure. An elevated resistive index of the hepatic artery may be useful for predicting the patient's clinical outcome and determining the need for a liver transplantation in patients with acute viral hepatitis.

Increasing bilirubin and decreasing ALT, increasing creatinine are associated with poor prognosis of fulminant HAV, this in agreement with *Ryan M et al., 2006* they found high serum creatinine, lower ALT and lower alkaline phosphatase are associated with transplant or death. These results may reflecting severe necrosis.

Decreasing albumin level, prolonged prothrombin time, presence of ascites and higher grades of encephalopathy are associated with high mortality among fuminant group, this in harmony with *Poddar U et al., 2002* who reported that Total serum bilirubin and grade of encephalopathy were significantly higher, serum albumin was significantly lower, and prothrombin time was significantly prolonged in those who died than the recovered.

CONCLUSION

A major benefit of this study is that early prediction of FHF can be predicted by simple tests and appropriate medical treatment could block further liver destruction and prevent development of FHF. Also, the importance of proper health education and of HAV vaccination could prevent the occurrence of HAV infection in children and its subsequent complications (FHF).

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