Profile of viral hepatitis patients in Dakhliya, Oman

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ABSTRACT

Objectives: With the availability of routine serological diagnosis of all the major forms of viral hepatitis, namely, A, B, C, D, E consequent to initiation of National Viral Hepatitis Surveillance, the twin objective of the study was to assess the trend of various types of viral hepatitis and analyze the profile of the patients in the region of Al Dakhliya.

Methods. A one year prospective cohort, of all the suspects of viral hepatitis enrolled from 01/08/2003 to 31/07/2004 involving all health facilities (a total of 18 health institutions) of Dakhliya region, Sultanate of Oman, was subjected to centralized laboratory confirmation. Notification of viral hepatitis confirmed cases was the tool for analysis. A subset of unconfirmed viral hepatitis cases that were admitted and discharged from the referral hospital were retrieved and analyzed utilizing their computerized hospital records.

Results. There was a shift of incidence of hepatitis B towards higher age groups (32.4 ± 16.2 years) with only one case under 15 years of age ($p<0.0001$). While as under 15 year age group was less prone to hepatitis C ($p<0.05$), it had a high incidence for hepatitis A with mean age 11.4 ± 13.9 years ($p<0.01$). Hepatitis E incidence had a higher mean age of 44.6 ± 24.1 years with insignificant linear trend ($p>0.05$).

Conclusion. Progress in decline of viral hepatitis B has occurred at a rapid pace during the last decade following successful intervention of immunization against hepatitis with an almost 100% coverage. Affliction of younger age groups to hepatitis A is indicative of continued transmission of the disease in the community demanding improvements in preventive practices to curb any impending outbreak.

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Viral hepatitis is a disease of antiquity, but evidence for more than one etiologic agent has been recognized only since the 1940s, when 2 viruses [hepatitis A virus (HAV) and hepatitis B virus (HBV)] were thought to account for all disease. In the past 20 years, 3 additional hepatitis agents [hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV)] have been discovered, and there is evidence for at least one additional virus. Each of the 5 recognized hepatitis viruses belong to a different virus family, and each has a unique epidemiology.[1]

Estimates suggest that worldwide, there are 385 million carriers of hepatitis B virus and 170 million carriers of hepatitis C virus. More than 1 million deaths each year are attributable to hepatitis B. Transmission is mainly oro-fecal for hepatitis A and E, percutaneous for hepatitis B, C and D and sexual for hepatitis B. The course of the disease may be fulminating (namely, hepatitis E in pregnancy); chronic infection and severe sequelae occur for hepatitis B, C, and D.[1] Hepatitis A virus; HBV; HCV; HDV, which requires coexisting HBV infection; and HEV cause 95% of cases of acute

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viral hepatitis observed in the United States of America.[2] Whether hepatitis G virus (HGV) is pathogenic in humans remains unclear.

In previous reviews of viral hepatitis in Oman, recognized infectious hepatitis were classified as hepatitis A, B and "non-A, non-B." The latter were unrecognized or uncharacterized types of hepatitis and classified as hepatitis (Others).[3] Hepatitis B vaccination was introduced since August 1990 under the Program for Immunizations (EPI) with a phenomenal coverage of almost 100% in the target population.[4] Probability of source of infection and transmission dynamics in those "non-A, non-B" cases used to be hypothesized epidemiologically but could not be authenticated by laboratory, which was a major shortcoming. This limitation has been overcome considerably by the availability of centralized laboratory tests for all viral hepatitis under the Viral Hepatitis Surveillance.

Methods. Serological diagnosis under Viral Hepatitis Surveillance for various types of viral hepatitis, namely, A, B, C, D, E was initiated only in July 2003, to be performed at the only centralized public health laboratory in the capital of Oman. Under the policy all the blood samples of acute viral hepatitis suspects from various regions of the Sultanate are subjected to sequential screening, namely, after initial screening of a batch of samples for anti HAV immunoglobulin M (IgM) detection, only those found negative are subjected to hepatitis B surface antigen testing in the next lot. Likewise, samples negative for Australia antigen are further tested for hepatitis C antibodies (performed by Enzymed Linked Immunosorbent Assay) and those negative are finally tested for anti HEV IgG. All the HBsAg positive samples are subjected to hepatitis D testing to rule out coexisting infection.

Suspected viral hepatitis case definition adopted under the Viral Hepatitis Surveillance is broad to avoid underdiagnosis at the peripheral institution levels. Any acute illness typically including acute jaundice, anorexia, and malaise with laboratory indices of increased bilirubin and or elevated alanine aminotransferase levels is to be suspected as acute viral hepatitis. Central Public Health Laboratory communicated the results, either positive or negative to the Regional Hospital Laboratory, after one week of receipt of the sample for hepatitis A, after 2 weeks for hepatitis B, after 3 weeks for hepatitis C and after 4 weeks for hepatitis E. Results for coexisting hepatitis D among hepatitis B positive is received after 3 weeks along with results for hepatitis C. This weekly testing of the batch of samples enables a large number of specimens to be put simultaneously for testing, thereby ensuring cost effectivity.

Results. Consequent to introduction of hepatitis B vaccination under the National Immunization Schedule in August 1990, there has been a significant decline in the absolute number of hepatitis B cases especially in age groups less than 15 years as evident from **Table 1**. A low regional Population Proportion Rate (PPR) of 0.08/10,000 for hepatitis B in ages <15 years is reflected in **Table 2**.

Viral Hepatitis Surveillance policy is in the Sultanate of Oman for establishing a laboratory diagnosis of suspected viral hepatitis patients since July 2003. An insight into the data of Al Dakhliya region after completion of the first year of Viral Hepatitis Surveillance, revealed 73 (43.4%) laboratory confirmed viral hepatitis cases out of a total of 168 suspects from all the 19 health facilities (including the regional hospital) of the region.

Among 73 laboratory confirmed cases, hepatitis A incidence was higher in ages less than 15 years (73.6%). Hepatitis C incidence was higher in ages above 50 years (66.6%). The mean ages of affliction were 11.4 years ± 13.9 for hepatitis A and 50.7 years ± 25.2 for hepatitis C. The linear association

Age group	Years								
	1995	1996	1997	1998	1999	2000	2001	2002	2003
0 - <1 yr	1	1	5	4	1	0	0	0	1
1 - <4 yrs	183	105	153	72	1	3	4	3	2
5 - <9 yrs	220	120	116	57	16	7	8	6	2
10 - <14 yrs	47	41	39	33	10	2	6	3	2
15 - <19 yrs	39	35	30	24	12	12	8	11	5
20 - <24 yrs	36	27	31	19	10	3	11	10	16
24 - <34 yrs	36	44	37	35	16	7	5	7	13
35 - <44 yrs	24	26	26	24	3	7	6	3	10
> 45 yrs	36	38	62	45	16	8	11	10	14
Grand total	**622**	**437**	**499**	**313**	**85**	**49**	**59**	**53**	**65**

Table 1 - Age wise hepatitis B surface antigen (HBsAg) positive cases from year 1995 through year 2003 in Oman.

Table 2 - Population proportion rates (PPR) stratified by age group of confirmed viral hepatitis patients from August 2003 through July 2004 in the region.

Viral Hepatitis	Age group									Total		X^2	*p* value
	n	(%)	PPR*	n	(%)	PPR	n	(%)	PPR	n	(%)		
A	14	(73.6)	1.19	4	(21)	0.28	1	(5.2)	0.37	19		9.9	0.001
B	1	(3.3)	0.08	23	(76.6)	1.62	6	(20)	2.26	30		17.5	0.00003
C	2	(16.6)	0.17	2	(16.6)	0.14	8	(66.6)	3.01	12		4.5	0.03
E	1	(8.3)	0.08	6	(50)	0.42	5	(41.6)	1.88	12		0.08	0.76
G Total	**18**	**(24.6)**		**35**	**(47.9)**		**20**	**(27.3)**		**73**	**(100)**		

*Population proportion rate (PPR) calculated per 10,000 population

Viral hepatitis	Male		Female		Total		X^2 (Mantel-Haenszel)	*p* value
	n	(%)	n	(%)	n	(%)		
A	11	(57.8)	8	(42.1)	19	(100)	0.2	0.65 (NS)
B	19	(63.3)	11	(36.6)	30	(100)	1.9	0.15 (NS)
C	4	(33.3)	8	(66.6)	12	(100)	2.3	0.12 (NS)
E	5	(41.6)	7	(58.3)	12	(100)	0.7	0.37 (NS)
Grand total	**39**	**(53.4)**	**34**	**(46.5)**	**73**	**(100)**		

Table 3 - Gender distribution of confirmed viral hepatitis cases from August 2003 through July 2004 in the region.

SN	Disease category	n	(%)
1	Viral hepatitis not notified	2	(3.4)
2	Hepatomegaly (not classified elsewhere)	2	(3.4)
3	Chronic liver dysfunction / alcoholic hepatitis/	10	(17.2)
4	F/U cases of diabetes / HT with raised liver enzymes	7	(12)
5	Pyrexia of unknown origin	3	(5.1)
6	Chronic cardiac dysfunction (CHF, Pulmonary edema)	6	(10.3)
7	Chronic liver dysfunction (cirrhosis etc)	4	(6.8)
8	Abdominal pain (appendicitis, pancreatitis, retained placenta, cholecystitis)	11	(18.9)
9	Miscellaneous (multiple sclerosis, Sjogren`s syndrome, tonsillitis, arthritis, tuberculosis of the spine, road traffic accidents)	10	(17.2)
10	Sickle cell disease crisis	3	(5.1)
Grand total		**58**	**(100)**

F/U - follow-up, HT - hypertension, CHF - congestive heart failure

Table 4 - Disease profile of unconfirmed cases of viral hepatitis from referral hospital of the region.

of hepatitis A with decreasing age was significant $p<0.01$ and hepatitis C with increasing age was significant $p<0.0$. In spite of relatively negative skew of mean towards middle age, namely, 32.4 ± 16.2 years, linear association of hepatitis B with increasing age was very highly significant ($p<0.001$). A very significant linearity is explained by a high PPR of 2.26 per 10,000 population in >50 years compared to PPR of 1.62 in 15-50 age group and 0.08 per 10,000 population in 1 <15 years age groups. Hepatitis E incidence had a mean age of namely, 44.6 years ± 24.1 without any linear trend ($p>0.05$). It is clear from **Table 2** that no sample of confirmed HBsAg tested positive for coexisting hepatitis D.

From **Table 3** it is evident that no particular gender was predominantly associated with any type of Hepatitis ($p>0.05$). Out of the entire 73 confirmed viral hepatitis cases majority were locals (94.5%). Four expatriate patients had hepatitis A in 3 of them and hepatitis B in the remaining. Among remaining 95 unconfirmed cases, out of a total of 168 suspected cases, 58 suspects had been admitted to the regional hospital. As regional hospital patient database was computerized, it was possible to access the records of those 58 cases for their profile and final diagnosis. On analysis it was found that most of these cases, namely, 52 out of 58 cases (90%) belonged to 15 years or more age group with overall male predominance (60.3%). As per the record analysis of those 58 patients, final diagnosis at the time of discharge from the hospital was hepatomegaly (not classified elsewhere) in 3.4% of cases and various other conditions as shown in **Table 4** in 93.2%. Notification was missed in 2 cases (3.4%). All of the cases had bilirubin and/or either of the hepatic enzymes, namely, alanine transaminase, aspartate transaminase and alkaline phosphatase raised with or without the symptoms of hepatitis provoking the physicians to undertake Viral Hepatitis Surveillance as one of the investigations.

Discussion. Liver function is assessed by a battery of tests, which generally include a minimum of plasma bilirubin, albumin, and the enzymes alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase. Among the biochemical measures of liver function are cytoplasmic and mitochondrial enzymes such as ALT and AST while as alkaline phosphatase and gamma glutamyl transferase are membrane-associated enzymes. Alanine transaminase is more liver specific than AST and rises more than AST in early hepatocellular injury. The AST is raised more in chronic injury. Alkaline phosphatase and gamma glutamyl transferase, anchored to the biliary canaliculus, are raised in biliary outflow obstruction rather than hepatocellular damage. Serum bilirubin represents biochemical measure of liver function to commonly assess (i) hepatic anion transport; less than 5% of serum bilirubin is normally conjugated (ii) abnormal protein synthesis viz hypoalbuminemia in chronic liver injury; increased Prothrombin time viz cholestasis wherein synthesis of coagulation factor V, fibrinogen and vitamin K dependent Factors II (prothrombin), VII, IX and X is impaired.

Recommended case definition by Pan American Health Organization entails clinical description of acute illness typically including acute jaundice, dark urine, anorexia, malaise, extreme fatigue, and right upper quadrant tenderness. Biological signs include increased urine urobilinogen and >2.5 times the upper limit of serum ALT.[5] The definition adopted by us has included any significant increase in bilirubin and or elevated alanine aminotransferase levels. Urinary bilinogen assessment was excluded considering operational constraints.

Appropriate laboratory criteria suggested for etiological diagnosis of hepatitis A is IgM anti-HAV positive; for hepatitis B - IgM anti-HBc positive with or without HBsAg; for hepatitis C - anti-HCV positive; for hepatitis D - HBsAg positive/IgM anti-HBc positive plus anti-HDV positive and for hepatitis E - IgM anti-HEV positive.[5] The anti-HBc IgM test, specific for acute infection of viral hepatitis B, is not available in most developing countries for mass use due to its high cost. Thus instead of recommended anti-HBc IgM test in addition to the HBsAg for actual estimation of acute hepatitis B, only the latter was performed. Although HbsAg cannot distinguish between acute new infections and exacerbations of chronic hepatitis B, it certainly can give a trend of the prevalence of infection. As is amply clear from **Table 1** hepatitis B has shown a decline especially in the younger age groups in the country. Sparing younger ages in the region is reflective that the decline is realistic. Bias attributable to the laboratory diagnosis can be considered minimal considering the fact that laboratory confirmation of hepatitis B has been performed uniformly and consistently only by HBsAg testing through all the years post introduction of hepatitis B immunization. Likewise decision to determine hepatitis E positivity by demonstration of hepatitis E IgG anti-HEV instead of hepatitis E IgM anti-HEV was based on the availability of the resources and considering the prime objective of assessing the trend and not actual estimation.

In the past transfusion of blood and blood products was an important source of HCV transmission, but currently high-risk drug and sexual exposures account for most HCV transmission. Hepatitis C virus infection affects persons of all ages, but most acute cases of hepatitis C and the highest prevalence of anti-HCV are found

among young adults.[6] Blood banks screen blood to insure the safety of the blood supply. This has greatly reduced the number of hepatitis B and C cases resulting from transfusions and could explain the number of cases sparing younger ages with a trend to taper off in older age groups as evident by the significant linear association with increasing age ($p<0.05$).

Transmission of hepatitis A is primarily oro-fecal and predominant in developing countries in areas without sufficient sanitation. Higher infection rates also exist in settings where fecal-oral spread is likely, such as daycare centers. Routine vaccination of children is the most effective way to reduce hepatitis A incidence nationwide over time. Vaccination of children living in states and communities with consistently elevated rates of hepatitis A will provide protection from disease and is expected to reduce the overall incidence of hepatitis A.[7] Continued minimal transmission of hepatitis A in the region was evident by the mean age affliction of 11.4 years ± 13.9, which was significant compared to older age groups ($p<0.01$). Hepatitis E virus is transmitted primarily by the fecal-oral route, with fecally contaminated water providing the most common means of transmission. Transmission by person-to-person contact is undocumented. No evidence of chronic infection has been detected in long-term follow-up of patients with hepatitis E. Children below 14 and adults above 55 are prone to develop a subclinical form without jaundice.[8] In our study, PPR per 10,000 is highest (1.88) in ages >50 years followed by 0.42 cases per 10,000 but minimal (0.08) in age group of 15 – 50 and <15 years.

Follow up of referred unconfirmed viral hepatitis cases to the regional hospital (n=58) revealed various conditions, which may mimic a suspect of viral hepatitis. Establishing HGV as an etiologic agent for those cases was well outside the purview of the study as little is known about the relation of the newly discovered HGV to the cause and clinical course of acute and chronic viral hepatitis. Coexistent infection with HGV did not lead to chronic disease and did not affect the clinical course in patients with hepatitis A, B, or C evidence from the surveillance study of Alter et al,[9] which does not implicate HGV as an etiologic agent of non-A-E hepatitis.

Hepatitis F virus has been described in only a handful of cases (from France) with subsequent experimental transmission to primates. The virology, epidemiology, hepatotrophicity and clinical importance of HFV are quite uncertain.[10] Thus, a low PPR of 0.08 per 10,000 for hepatitis B in ages <15 years in the region is reflective of overall decline of hepatitis B cases in the country subsequent to the introduction of hepatitis B vaccination under EPI. The lower mean ages of affliction for hepatitis A in the region (11.4 years ± 13.9) indicates persistence of infection in the community with a potential of an outbreak. There may be varied circumstances leading to raised liver enzymes, which may not necessarily indicate hepatitis due to viral etiology. Compliance of stringent case definition for Viral Hepatitis Surveillance could enhance cost effectivity.

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