HEPATITIS D: EPIDEMIOLOGY IN SOUTH AUSTRALIA 2005-2014

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Introduction

Hepatitis D is a spherical virus with a diameter of about 36nm and is the smallest virus known to infect humans. It is a single stranded RNA virus with an internal core of delta antigen surrounded by an envelope derived from hepatitis B virus surface proteins. HDV(hepatitis D virus) infection can occur either through coinfection at the same time as HBV transmission or through superinfection in someone who is already known to be HBV(hepatitis B virus) positive (1). Similar to HBV, HDV is transmitted parenterally through exposure to infected blood or bodily fluids. In highly endemic areas, intra-familial spread is common (2).

Although HDV suppresses the replication of HBV , acute HDV can lead to acute liver failure. Chronic HDV can expedite progression of liver disease leading to cirrhosis, hepatic decompensation and increase the risk of liver cancer (3). Chronic hepatitis related to HDV is difficult to treat. The only therapy known to show response are conventional and pegylated interferon (4). The response varies between 15-50% sustained virological response (SVR) and comparison studies are difficult given limited patient numbers (5).

It is estimated that there are 240 million individuals chronically infected with HBV worldwide. This includes 15-20 million individuals co-infected with HDV(6) with an overall prevalence rate of 5% of all HBsAg carriers. HDV is rare in developed countries where the disease seemed to be limited to intravenous drug users(IVDU). Higher prevalence of this disease is seen in South America and Africa(7). Genotype I is the most widespread geographically, having been identified in North America, Europe and the Middle East. Genotype II has been found in East Asia and genotype III is found exclusively in South America(8).

The prevalence of HDV in Australia is presumed to be low. However data in the local literature is extremely limited. From the annual reports of the National Notifiable Disease System Surveillance (NNDSS) it is estimated that 20-30 new cases of HDV are notified each year. However the most recent report in 2013 found a rise in the number of new diagnoses to 53 new cases with four new cases reported in South Australia (9).

Over the last two decades, there has been only one local study conducted in Victoria looking at the epidemiology of HDV in Australia(1). No previous studies have been conducted in South Australia to determine the local epidemiology of HDV. This study aims to establish the pattern of disease in South Australia. The conclusion from this study should be used as a guide for future studies in South Australia to better establish the pattern and natural history of infection as well as to identify the predominant genotype distribution of HDV locally.

Materials and Methods

Laboratory

Data regarding HDV diagnoses made between January 2005 and December 2014 were obtained from the South Australian (SA) Pathology testing records.

Details of patients reviewed at the Royal Adelaide Hospital either through the Infectious Disease or Viral Hepatitis Clinic were identified.

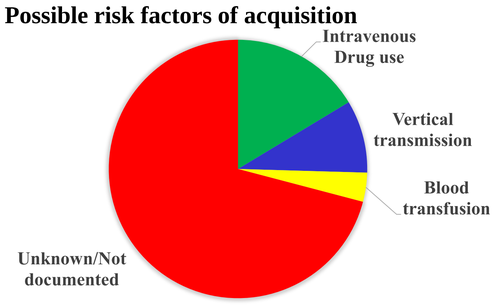
Clinical

Patient's medical records were retrieved and reviewed for information relating to epidemiology, risk factors and markers of disease severity.

Results

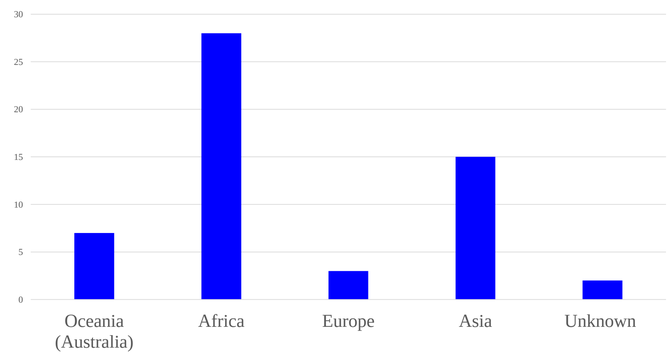
Between 2005and 2014, there were 167 HDV Ab positive test results within 119 patients identified through SA Pathology records. Fifty five patients were identified as being followed up at the Royal Adelaide Hospital (RAH). The majority of cases were in men (76%) and the median age of diagnosis was 40 years (interquartile range (IQR) 32-54 years). Intravenous drug use was reported as a risk factor for transmission in nine subjects (16.4%), vertical transmission in five and blood transfusion in two. The remainder of the risk factors were unknown or not documented

Figure 1: Possible risk factors of acquisition



From the information available, most patients were born overseas (46 out of 55 patients, 83.6%). The majority were from Africa (50.9%) predominantly from Western Africa (35.7%) and North Africa (35.7%)

Figure 2: Continents of Origin

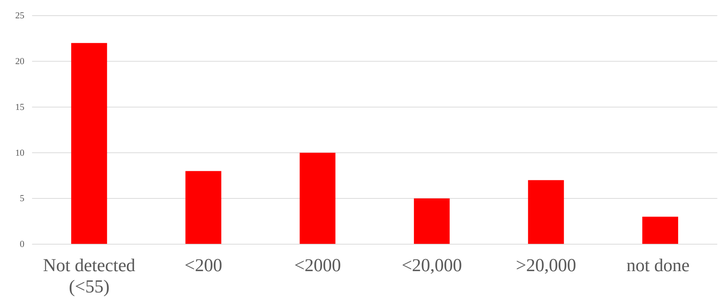


From the fifty five patients followed up at the Royal Adelaide Hospital, only fifteen patients (27.3%) were having active follow up in hospital at the time of the review. About half the patients seen (27/55, 49%) did not attend subsequent appointments and were lost to follow up. Four patients were negative for HDV Ab on subsequent testing indicating a possible laboratory false positive. Three patients moved interstate and their ongoing care was taken over by a different provider. One patient moved out of the public area and was treated privately by an Infectious Disease physician. Five patients were deceased. Among the patients seen at the Royal Adelaide Hospital, only thirty (54.5%) patients were tested for HDV by PCR. Fourteen patients had detectable HDV RNA with eight patients subsequently tested for quantitative viral load. Among the sixteen patients with undetectable HDV RNA, only five patient had repeat testing for RNA levels.

Investigations

The presence of hepatitis B eAg (HBeAg) correlates with hepatitis B virus infectivity. The patients' hepatitis B eAg/eAb status was evaluated in the study. Results were consistent with majority of the patients testing positive for hepatitis B eAb (47/55, 84.5%), suggesting relative suppression of the HBV. Hepatitis B viral load results were obtained prior to patients commencing treatment and results demonstrated a low level of viremia consistent with suppression of HBV replication

Figure 3: Hepatitis B viral load prior to treatment initiation



Patient treatment and outcomes

Fourteen patients (25.4%) patients with HBV/HDV co-infection had anti-viral treatment. Three patients were treated with 48 weeks of pegylated interferon therapy for HDV infection. One patient only had HDV PCR test performed post treatment therefore the indication for treatment was unclear. Another patient had an undetectable PCR at the end of therapy but repeat PCR testing was not performed. The third patient relapsed 12 months post treatment and subsequently was commenced on entecavir therapy due to a rising HBV viral load.

Eleven other patients were on treatment primarily targeting their HBV with four also on treatment for other co-infecting viruses. Three patients who were co infected with HIV were on tenofovir/emtricitabine (Truvada) for concurrent treatment. One patient who was co infected with hepatitis C was commenced on a trial medication for hepatitis C infection.Three patients developed Hepatocellular carcinoma, two of whom died during the period studied. One patient had transcatheter arterial chemoembolization (TACE) with control of the cancer and was commenced on entecavir post procedure.

Discussion

This study is consistent studies from other developed countries where migration is recognised as the highest risk factor for HDV infection, with a small proportion of local acquisition through intravenous drug use. Breakdown of data into individual patient's pattern of testing was inconsistent due to poor patient follow up with no trend of viral load or repeat PCR testing being established. There are no established guidelines in place for screening and monitoring HDV in the setting of untreated HBV which probably explains the inadequacy of testing by clinicians in this population.

Hepatitis B viral load results prior to treatment initiation demonstrated an overall low rate of viremia consistent with suppression of replication of HBV when it co-exists with HDV. Among the small number of patients (3/55) who received interferon therapy for HDV, the success rate was not clear. Currently, there are many trials focussing on treating Hepatitis D. As this study was a retrospective review, there are many limitations to it.

Conclusion

The incidence and prevalence of chronic HDV and long term sequelae of the infection is expected to rise in Australia due to migration. Although testing for HDV has risen, not all patients with HBV infection get routinely tested for HDV. It is important that clinicians have better guidance to ensure testing and appropriate follow up for patients with HBV and HDV infection.

References

1. Shadur B, MacLachlan J, Cowie B. Hepatitis D virus in Victoria 2000-2009. Intern Med J.2013
2. Alves C, Branco C, Cunha C. Hepatitis delta virus: a peculiar virus. Adv Virol.2013
3. Noureddin M, Gish R. Hepatitis delta: epidemiology, diagnosis and management 36 years after discovery. Curr Gastroenterol Rep.2014
4. Niro GA, Rosina F, Rizzetto M. Treatment of hepatitis D. Journal of Viral Hepatitis. 2005.
5. Yurdaydin C. Treatment of chronic delta hepatitis. Semin Liver Dis. 2012
6. Abbas Z, Abbas M. Management of hepatitis delta: Need for novel therapeutic options. World J Gastroenterol. 2015
7. Alfaiate D, Deny P, Durantel D. Hepatitis delta virus: From biological and medical aspects to current and investigational therapeutic options. Antiviral Res. 2015
8. Altuglu I, Ozacar T, Sertoz RY, Erensoy S. Hepatitis delta virus (HDV) genotypes in patients with chronic hepatitis: molecular epidemiology of HDV in Turkey. Int J Infect Dis. 2007
9. Australia's notifiable disease status, 2013: Annual report of the National Notifiable Diseases Surveillance System. Commun Dis Intell Q Rep. 2015