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The medical impact of hepatitis D virus infection in Uzbekistan

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Abstract

Background & Aims: The hepatitis B virus (HBV) is endemic in Uzbekistan but the medical impact of infection with the HBV-dependent hepatitis D virus (HDV) is unknown in the Country. An Hepatology Center was recently established at the Institute of Virology in Tashkent, which has set up a database enlisting patients with chronic viral liver disorders from all over Uzbekistan; it provides an observatory on the current scenario of viral hepatitis in the Country.

Methods: The prevalence of HBV monoinfection, hepatitis C virus (HCV) infection and HDV superinfection on hepatitis B surface antigen (HBsAg)-positive cirrhosis was determined in 6589 patients with viral cirrhosis collected in the last 3 years.

Results: Of 1089, 1150 and 1455 carriers of the HBsAg with cirrhosis recruited in 2016, 2017 and 2018, 834 (76.5%), 926 (80.5%) and 1224 (84%) respectively, had antibody to the HDV. In 2016, 2017 and 2018, the prevalence of HDV infection has been 41%, 45% and 49.1% respectively, largely exceeding the prevalence of HBV monoinfection (12.5%, 11% and 9.3% respectively) and surpassing the prevalence of HCV in 2017 and 2018 (44% and 41.5% respectively). The median age of the patients with HDV cirrhosis was 39 years, distinctly lower than that of HBV and HCV patients (46 and 55).

Conclusions: Superinfection with the HDV is present in over 80% of the HBsAg-positive cirrhosis in Uzbekistan. The HDV appears to be the major cause of advanced viral liver disease and of juvenile cirrhosis in the Country.

KEYWORDS
cirrhosis, epidemiology, HBV, HDV

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1 | INTRODUCTION

The hepatitis D virus (HDV) is a liver pathogen dependent on the hepatitis B virus (HBV). It can only cause chronic infection by superinfection of HBV carriers and for this reason its epidemiology parallels that of the HBV.[1] Despite the high endemicity of the HBV in Central Asia, the impact of HDV infection in this macro-area is largely unknown, in contrast to its major medical role in surrounding Iran,[2] Pakistan[3] and Mongolia.[4]

Fragmentary studies suggested that Central Asia may also bear the brunt of hepatitis D,[5-7] but these studies were usually published in the local press and went unnoticed by the global scientific community; so far the issue of hepatitis D in the area has

Abbreviations: Anti-HCV, antibodies to hepatitis C virus; anti-HD, antibodies to hepatitis D virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus..

not attracted international interest and was not comprehensively investigated.[8]

With a population of almost 32 million and an HBV prevalence of about 13%,[9] Uzbekistan is aggravated by the highest burden of hepatitis B surface antigen (HBsAg)-positive liver diseases in Central Asia. These have so far been attributed to ordinary HBV infection; in 2001, Ruzibakiev referred to the HDV as an infection of unknown prevalence in Uzbekistan and no major survey has since been performed.[10]

A Hepatology Center was established in the last years at the Institute of Virology in Tashkent; in 2018, it has received official recognition as the National Referral Center for Viral hepatitis.[11] The Center has created and maintains a database where all afferent patients are registered. The patients are tested for HBV, HDV and hepatitis C virus (HCV) markers, and the HBsAg positive are further tested for markers of HDV infection.

This paper reports how the systematic testing for HDV in cirrhotic patients is dramatically changing the perception of the scenario of HBsAg-positive liver diseases in Uzbekistan.

Keypoints

- The hepatitis B virus (HBV) is endemic in Uzbekistan but the medical impact of infection with the HBV-dependent hepatitis D virus (HDV) is unknown in the Country.
- An Hepatology Center was recently established at the Institute of Virology in Tashkent, providing an observatory on the current scenario of viral hepatitis in the Uzbekistan.
- Superinfection with the HDV is present in over 80% of the HBsAg-positive cirrhosis in Uzbekistan, exceeding also the prevalence of HCV infection.
- The HDV appears to be the major cause of advanced viral liver disease and of cirrhosis in young adults in Uzbekistan.

2 | MATERIALS AND METHODS

2.1 | Patients

From the beginning of 2016 to the end of 2018, 6589 patients with viral cirrhosis were referred from all over Uzbekistan to the Hepatology Center, 3755 as out-patients, 2834 as in-patients hospitalized at the Clinical Department of the Institute of Virology.

The diagnosis of cirrhosis was based on a liver biopsy, on liver stiffness in elastography (FibroScan®, Echosens) or on abnormal liver biochemistry/liver echography/physical signs typical of cirrhosis.

All the patients, whether out-patients or in-patients, were tested or retested for HBV and HCV infections with the determination of the HBsAg and of antibodies to the HCV (anti-HCV) in serum; all those positive for the HBsAg were further tested for antibodies to the HDV (anti-HD).

The demographic, clinical and serological details were determined in 138 consecutive patients with HDV cirrhosis hospitalized at the Clinical Department of the Institute of Virology of Tashkent in 2018; a diagnostic liver elastography was performed in all and 23% were further submitted to a liver biopsy.

TABLE 1 Viral aetiologies in 6589 cirrhosis recruited from all over Uzbekistan at the Clinical Department of the Tashken Institute of Virology, 2016-2018

Year	HBV	HDV	HCV
2016	255 (12.5%)	834 (41%)	947 (46.5%)
2017	224 (11%)	926 (45%)	912 (44%)
2018	231 (9.3%)	1224 (49.1%)	1036 (41.6%)

Note: Data are reported as N (%).
Abbreviations: HBV, hepatitis B virus monoinfection; HCV, hepatitis C virus infection; HDV, hepatitis D/HBsAg coinfection.

The majority of them were tested for serum HBV-DNA and HDV-RNA.

2.2 | Serology

Testing for the HBsAg was performed with DS-EIA-HBsAg and for anti-HCV with DS-EIA-anti-HCV (Diagnostic Systems, Nizhny Novgorod, Russia). Testing for anti-HD was performed with DS-EIA-anti-HD (Diagnostic Systems) and with DAB-CE, total antibody to HDV (DIA-PRO).

To determine HBV-DNA and HDV-RNA in serum, the Amplisens HBV-FL and Amplisens HDV-FL assays (Amplisens) were used.

2.3 | Statistical analysis

Categorical and continuous variables were collected for descriptive analysis and reported as number (%) and median (range) respectively. Data distribution was evaluated by D'Agostino-Pearson test.

Data management and statistical analysis were performed with MedCalc® software, version 18.9. (MedCalc).

3 | RESULTS

3.1 | Prevalence of HDV in the total population of cirrhotics

Of the 6589 cirrhotic patients with positive viral serology, 710 had HBV monoinfection (HBsAg positive; anti-HD negative), 2895 had HCV infection (anti-HCV positive; HBsAg negative) and 2984 had HDV infection (HBsAg and anti-HD positive). Two hundred sera from HBV and HDV patients were tested in parallel with the DS-EIA anti-HD produced in Russia and with the DAB-CE anti-HD assay produced in Italy; the results were concordant in 99% of cases.

TABLE 2 Demographic and clinical features of 138 patients with HDV cirrhosis hospitalized at the clinical Department of the Tashkent Institute of Virology in 2018

Characteristics		No. of patients evaluated
Demography		
Median age (y)	39 (18-53)	138
Gender (males/females)	100/38 (72%)	138
Education (high/secondary)	4/130 (3%)	134
No. of family components	6 (2-9)	104 households
Risk factors		
Blood transfusion	29 (15%)	130
Major surgery	10 (7.5%)	131
Drug addiction	1 (0.9%)	110
Alcohol	1 (0.9%)	110
Habitudinal mercenary sex	0	41
Serology		
HBV-DNA positivity	68 (83%)	82
Median titre	$5.3x10^3$ ($11-3.3x10^5$) IU/mL	
Low titre (<$2x10^4$ IU/mL)	61 (90%)	
High titre (>$2x10^4$ IU/mL)	7 (10%)	
HDV-RNA positivity	87 (98%)	89
Median titre	1.7×10^6 (11×10^2-9.9×10^7) IU/mL	
Low titre (<10^3 IU/mL)	19 (22%)	
High titre (>10^3 IU/mL)	68 (78%)	
Child Pugh		
Class A	53 (38%)	138
Class B	69 (50%)	138
Class C	13 (12%)	138

Note: Data are reported as N (%) or median (range).
Abbreviations: HBV, hepatitis B virus; HDV, hepatitis D virus.

Of 1089, 1150 and 1455 carriers of the HBsAg with cirrhosis recruited in 2016, 2017 and 2018, 834 (76.5%), 926 (80.5%) and 1224 (84%) respectively had anti-HD. The number and relative percentage of the three viral infections in cirrhotics from 2016 through 2018 are shown in Table 1. The percentage of HBV patients decreased over the 3 years, it slightly decreased among the HCV patients in 2017 and then increased by 124 units from 2017 to 2018, it steadily increased among HDV patients with an increase in 2018 of 298 units over 2017. The number and percentage of HDV infections was the highest of the three viral infections both in 2017 and 2018, with 926 patients and a 45% in 2017 and with 1224 patients and a 49.1% in 2018.

3.2 | Demographic and clinical features of 138 hospitalized HDV cirrhotic patients

The male to female ratio was 72% (Table 2). The median age was 39 years (18-53); 27 patients were younger than 30 years. The median age of the HDV patients was compared with the median age of two separate series of 100 HBV and 113 HCV patients; the HBV group median age was 46 (18-75) and the HCV group median age was 55 (33-84).

Four of the patients had received high education. One patient admitted drug addiction, none admitted habitudinal mercenary sex. Fifteen per cent received blood transfusions and 7.5% had major surgery in the past. One patient was an alcoholic. The median number of members in the household, determined in 104 households, was 6 (2-9).

The Child Pugh score of the cirrhosis was A in 38%, B in 50% and C in 12% of the patients. Serum HBV-DNA was positive in 68 of 82 (83%) patients with a median titre of 5.3×10^3 IU/mL ($11-3.3 \times 10^5$); it was at a titre lower than 2×10^4 IU/mL in 61 patients and higher than 2×10^4 IU/mL in seven patients. Serum HDV-RNA was positive in 87 of 89 patients (98%) with a median titre of 1.7×10^6 IU/mL (11×10^2-9.9×10^7); it was at a titre lower than 10^3 IU/mL in 19 patients and higher than 10^3 IU/ml in 68 patients.

4 | DISCUSSION

Though the HBV is widespread in Uzbekistan, the contribution of the hepatitis D virus to the burden of HBsAg-positive liver disorders in the Country has not been assessed so far. Reviews published in the last few years on the regional impact of HBV by international agencies have ignored the issue of HDV and only recently the World Health Organization has mentioned Central Asia as an area with potentially high HDV endemicity.[8,9,12,13]

The newly established Tashkent Hepatology Center collects a large number of liver patients from all over the Country and has implemented the systematic testing of all HBsAg-positive patients for HDV markers: it thus provides an adequate observatory for the evaluation of the national scenario of HDV diseases.

Because the HDV is almost invariably pathogenic and induces liver disease,[14] the prevalence rate of its infection is distinctly higher in HBsAg carriers with chronic liver disease than in asymptomatic HBV infections and raises in parallel with the severity of the liver disease. The corollarium is that serological surveys for HDV are most reliable when evaluated in HBsAg carrier with advanced liver disorders, and that comparison of the prevalence of HDV vs HBV and HCV should be made on a common denominator of liver pathology, rather than on conventional demographic denominators.[15] On this basis, only the patients with cirrhosis collected at the Center were considered in this study.

Since the opening of the Hepatology Center, more than two thousand patients with viral cirrhosis were examined every year, of which more than a thousand had HBsAg and about a thousand

had HCV markers. However, the further systematic testing for HDV markers has shown that from 76.5% to 84% of the HBsAg-positive cirrhotics collected from 2016 to 2018 had the HDV, this infection accounting for 40% to 50% of the total cases of cirrhosis. Most of the patients had a Child Pugh A and B cirrhosis. Only a minority had an advanced decompensated Child Pugh C cirrhosis; this type of patients was usually not referred either because they were directly sent to intensive care unit or, with no liver transplant program in the Country, they were attended locally with palliative care.

Surprisingly, therefore, the data of this study indicate that chronic hepatitis D is a major cause of advanced liver disease in Uzbekistan, largely exceeding in the Tashkent series the prevalence of ordinary HBV disease and also surpassing the proportion of HCV cirrhosis in 2017 and 2018.

Chronic hepatitis D is recognized as the most severe form of viral liver disorders,[16] and this ominous prerogative is confirmed in the present study. The 39 years median age of the HDV patients was distinctly younger than the 45 and 55 years median age of two series of HBV and HCV cirrhotics, respectively; among the HDV cirrhotics, 27 were younger than 30 years. The significant difference in the age specific prevalence between HDV and HBV/HCV cirrhotics indicates that hepatitis D runs a more rapid course to cirrhosis and liver failure then the other viral infections and represents a major cause of mortality in young adults in Uzbekistan. Interestingly, in their analysis of hepatitis B in 2000, Beutels et al,[17] unaware of the existence of hepatitis D in the Country, calculated that 25% of the deaths between 30 and 40 years in Uzbekistan were because of hepatitis B. Our study, however, indicates that the major culprit of the relevant early mortality in the Uzbekistan population is hepatitis D and not hepatitis B.

Transmission of HDV was unrelated to recognized apparent parenteral or sexual exposure; only one of the HDV cirrhotics admitted drug abuse and a sexual risk from promiscuous and mercenary sex was not reported by the patients. In Uzbekistan transmission of HBV is predominantly horizontal and occurs mainly in childhood, as is common in areas where the HBV remains highly endemic.[18,19]

Considering the young age of most of the cirrhotic patients when they acquired HDV infection and in analogy with the transmission pattern in other areas with a high HBV endemicity,[20] the virus has most likely spread as a secondary superinfection event in preadolescent children and in adolescents who acquired the HBsAg state early in life. Close interpersonal contacts within the household were presumably the major mode of transmission; many households of the index cases of this study included more than five members and household crowding is recognized as a major factor permissive of contact transmission of the HDV among intrafamily clusters of the HBsAg.[21]

Unsafe medical practices are a second important risk factor for HDV transmission in Uzbekistan: it was usual practice before the beginning of the 2000s to reuse unsterilized needles for injections and the use of injectable drugs that are sold without prescriptions and are used without special control, remains common in the Country even for treating minor diseases (E. Musabaev, personal communication).

The clinical outcome of HDV superinfections is determined not only by the prevalence rate of the HBsAg in the population but also by the local environmental conditions. In the most disadvantaged scenarios of the native populations of the Amazon basin in South America and of Central Africa where the HDV was highly pervasive since infancy,[20] the virus spread rapidly in children and adolescents facilitated by lack of hygiene, resulting in increased virulence and devastating outbreaks of fulminant hepatitis at young ages.[22,23]

Though the prevalence of HBV is high in Uzbekistan, the age specific prevalence of HDV disease was different and no major outbreaks of fulminant HBsAg hepatitis attributable to HDV have been reported in children. This suggests that the environmental conditions were adequate to retard contact transmission in childhood, this increasing further in adolescence in parallel with the increase of social promiscuity and the inception of sexual contacts.

In conclusion, the recognition of the important medical impact of HDV in Uzbekistan considerably changes the perspective of chronic HBsAg-positive liver diseases in the country; the course, prognosis and therapeutic options are different in the large majority of the HBsAg-positive liver diseases associated with HDV infection compared with the minority of ordinary HBV monoinfection. In view of the high prevalence of HDV in surrounding Iran, Pakistan and Mongolia, the finding in Uzbekistan may represent the paradigm of an important role of HDV throughout a large part of Asia. The disproportionate dimension of the HDV issue is raising a formidable medical problem in Uzbekistan. While HBV and HCV are now under control in the country with the low-cost direct antivirals, there is no resolutive therapy for hepatitis D; the use of the poorly efficacious Peg Interferon is limited by its prohibitive cost. New therapies may be on the horizon. While unable to eradicate the HDV in the short term, the HBsAg entry inhibitor Myrcludex B[24] and the farnesylation inhibitor Lonafarnib[25] given over the long term might provide a durable control of hepatitis D.

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CONFLICT OF INTEREST

The authors do not have any disclosures to report.

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REFERENCES

1. Smedile A, Rizzetto M, Gerin JL. Advances in hepatitis D virus biology and disease. In: Boyer JL, Ockner RK, eds. *Progress in liver disease*, vol. XII. Philadelphia, PA: WB Saunders; 1994:157-175.
2. Alavian SM, Alavian SH. Hepatitis D virus infection; Iran, Middle East and Central Asia. *Hepat Mon*. 2005;5:137-143.

3. Mumtaz K, Hamid SS, Adil S, et al. Epidemiology and clinical pattern of hepatitis delta virus infection in Pakistan. *J Gastroenterol Hepatol*. 2005;20:1503-1507.
4. Chen X, Oidovsambuu O, Liu P, et al. A novel quantitative microarray antibody capture assay identifies an extremely high hepatitis delta virus prevalence among hepatitis B virus-infected mongolians. *Hepatology*. 2017;66:1739-1749.
5. Abdukadirova M, Khikmatullaeva A, Musabaev E, Ibadullaeva N. Prognostic marker of liver fibrosis in patients with chronic viral hepatitis B and D. *European J Biomed Pharm Sci*. 2018;5:50-53.
6. Konysbekova A. Chronic viral hepatitis D – the current state of a problem. *J Clin Med Kazakhstan*. 2017;1:11-14.
7. Semenov AV, Ostankova YV, Nogoybaeva KA, et al. Molecular epidemiology features of HBV/HDV co-infection in Kyrgyzstan. *Russian J Infec Imm*. 2016;6:141-150.
8. Razavi-Shearer D, Gamkrelidze I, Nguen MH, et al. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modeling study. *Lancet Gastroenterol Hepatol*. 2018;3:383-403.
9. Hope VD, Eramova I, Capurro D, Donoghoe MC. Prevalence and estimation of hepatitis B and C infections in the WHO European Region: a review of data focusing on the countries outside the European Union and the European Free Trade Association. *Epidemiol Infect*. 2014;142:270-286.
10. Ruzibakiev R, Kato H, Ueda R, et al. Risk factors and seroprevalence of hepatitis B virus, hepatitis C virus, and human immunodeficiency virus infection in Uzbekistan. *Intervirology*. 2001;44:327-332.
11. Resolution of the Cabinet of Ministry of Uzbekistan. #537, July 24, 2017.
12. Maistat L, Kravchenko N, Nikelsen T, et al. Viral Hepatitis B and C in Eastern Europe and Central Asia: civil society response to the epidemic. Alliance for Public Health. www.aph.org.ua. Accessed July 27, 2017.
13. Hepatitis D. *WHO key facts*. https://www.who.int/en/news-room/fact-sheets/detail/hepatitis-d. Accessed 23 July, 2018.
14. Fattovich G, Giustina G, Christensen E, et al. Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B. *Gut*. 2000;46:420-426.
15. Rizzetto M. Hepatitis D virus. In: Wong RJ, Gish RG, eds. *Clinical Epidemiology of Chronic Liver Diseases*. Cham, Switzerland: Springer. 2019:135-148.
16. Farci P. Delta hepatitis: an update. *J Hepatol*. 2003;39:S212-S219.
17. Beutels P, Musabaev EI, Van Damme P, Yasin T. The disease burden of hepatitis B in Uzbekistan. *J Infect*. 2000;40:234-241.
18. Avazova D, Kurbanov F, Tanaka Y, et al. Hepatitis B virus transmission pattern and vaccination efficiency in Uzbekistan. *J Med Virol*. 2008;80:217-224.
19. Gray Davis L, Weber JD, Lemon SM. Horizontal transmission of hepatitis B Virus. *Lancet*. 1989;1:889-893.
20. Hadler SC, De Monzon MA, Bensabath G, Duran MM, Schatz G, Fields HV. Epidemiology of hepatitis delta virus infection in less developed countries. *Prog Clin Biol Res*. 1991;364:21-31.
21. Bonino F, Caporaso N, Dentico P, et al. Familiar clustering and spreading of hepatitis Delta Virus infection. *J Hepatol*. 1985;1:221-226.
22. Hadler SS, De Monzon MA, Ponzetto A, et al. An epidemic of severe hepatitis due to delta virus infection in Yupca Indians in Venzuela. *Ann Intern Med*. 1984;100:339-344.
23. Lesbordes JL, Ravisse P, Georges A, et al. Studies on the role of HDV in an outbreak of fulminant hepatitis in Bangui (Central African Republic). *Prog Clin Biol Res*. 1987;234:451-459.
24. Nkongolo S, Urban S. Entry inhibition with Myrcludex B: a promising future regimen for chronic hepatitis D virus infection. In: Rizzetto M, Smedile A, eds. *Hepatitis D Virology, Management and Methodology*. Rome, Italy: Il Pensiero Scientifico. 2019:329-342.
25. Yurdaydin C. New treatment options for delta virus :is a cure in sight? *J Viral Hepat*. 2019;26:618-626.

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