Rat hepatitis E virus and genotype 4 hepatitis E virus infections among immunocompromised persons and patients with hepatitis in Hong Kong: abridged secondary publication

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KEY MESSAGES

1. Rat hepatitis E virus is a major cause of hepatitis E among transplant recipients and immunocompromised patients in Hong Kong.
2. Most of these infections belong to a single strain group: LCK-3110.
3. Street rats in Hong Kong commonly harbour rat hepatitis E virus, although few carry LCK-3110-like strains associated with most human disease.
4. Both rat and genotype 4 hepatitis E virus variants frequently progress to chronicity in immunocompromised persons with poor response to immunosuppression reduction alone.
5. Chronic rat hepatitis E is curable with ribavirin; the genetic basis for non-susceptibility to ribavirin in genotype 4 hepatitis E virus is substantially different from genotype 3 hepatitis E virus.

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Introduction

Hepatitis E virus (HEV) is one of the most common causes of acute viral hepatitis in Hong Kong. HEV variants capable of infecting humans include swine HEV (HEV-A genotypes 3 and 4) and rat hepatitis E virus (HEV-C). These are the most common causes of hepatitis E in Hong Kong.[1,2] Infection with HEV-A genotype 3 is well studied in terms of rates of progression to chronicity and responses to ribavirin.[3] However, it is uncertain how humans acquire HEV-C infections from rats. Genomic epidemiological links between rat and human HEV-C strains are not well defined. We compared HEV-A and HEV-C infection prevalences among patients with hepatitis and transplant recipients in Hong Kong and in immunocompromised patients. Rates of HEV-C carriage in captured street rats were estimated.

Methods

Blood samples from patients with hepatitis and transplant recipients, along with rectal swabs from captured street rats, were tested for HEV-C RNA and/or HEV-A RNA. Some transplant recipients also provided 1-year follow-up samples; these were retrieved for HEV RNA screening and HEV immunoglobulin G testing to identify cases of asymptomatic seroconversion and subclinical infection. Sequencing was performed for human and rat HEV isolates, followed by phylogenetic analysis. Clinical characteristics of HEV-A genotype 4 and HEV-C infections in immunocompromised persons were compared.

Results

In total, six cases of HEV-C infection and 17 cases of HEV-A infection were identified among transplant recipients and patients with hepatitis. All six cases of HEV-C infection occurred in immunocompromised persons, whereas only five cases of HEV-A infection occurred in immunocompromised persons.

Between January 2016 and December 2020 in Hong Kong, 21 immunocompromised patients were infected with HEV-A genotype 4 (n=12) and/or HEV-C (n=13) [Table]. Both HEV-A genotype 4 and HEV-C active infections in immunocompromised persons frequently progressed to chronicity requiring antiviral therapy. Ribavirin generally achieved a good response in HEV-C infections. Ribavirin-refractory HEV-A genotype 4 infections were linked to mutations such as K1383N in the RNA-dependent RNA polymerase segment of the HEV genome, which was documented in all such patients. Most human HEV-C infections were due to a single strain group—LCK-3110—although infections from other strain groups were also documented, with diverse clinical phenotypes such as prolonged infection in the absence of immunosuppression.

Of 1161 street rats in Hong Kong, 72 (6.2%) had

detectable HEV-C RNA, but only two of these were confirmed to carry the LCK-3110 strain group. One of these rats was captured in Wong Tai Sin and the other in Wan Chai. A correlation between HEV-C epizootics and human infection was not established, although this could be due to the sporadic nature of sampling.

Discussion

HEV-C is an important cause of hepatitis E infection in transplant recipients and immunocompromised patient groups in Hong Kong. Most of these infections belong to a single strain group. Street rats in Hong Kong commonly harbour HEV-C, although few carry the LCK-3110-like strains associated with most human cases. Both HEV-C and HEV-A genotype 4 variants frequently progress to chronicity in immunocompromised persons with poor response to immunosuppression reduction. Chronic HEV-C infection is curable with ribavirin; the genetic basis for non-susceptibility to ribavirin for HEV-A genotype 4 is substantially different from HEV-A genotype 3.

Clinicians should test for HEV-C in hepatitis patients in Hong Kong, particularly in immunocompromised individuals. Immunosuppression reduction alone seldom resolves HEV-C infection in immunocompromised hosts, but oral ribavirin is an effective treatment.

Carriage of HEV-C was observed among captured street rats in Hong Kong, although no evidence was found for an active epizootic of the same HEV-C strain group causing human disease. Continued genomic surveillance and sequencing of HEV-C in rats and humans is required.

TABLE. Clinical characteristics of 21 immunocompromised patients infected with hepatitis E virus (HEV)-A genotype 4 and/or HEV-C.

Characteristic	Patients with HEV-A genotype 4 (n=12)*	Patients with HEV-C (n=13)*
Male sex	9 (75.0)	11 (84.6)
Mean age, y	52.8	54.9
Immunosuppressive condition		
Liver transplant	1 (8.3)	2 (15.4)
Kidney transplant	6 (50.0)	5 (38.5)
Heart transplant	1 (8.3)	1 (7.7)
Lung transplant	1 (8.3)	0
Haematopoietic stem cell transplant	1 (8.3)	1 (7.7)
Haematological malignancy	2 (16.7)	1 (7.7)
Advanced HIV	0	2 (15.4)
Rheumatic disorder	0	1 (7.7)
Hepatitis E outcomes		
Spontaneous resolution	0	1 (7.7)
Early ribavirin with sustained virological response	2 (16.7)	2 (15.4)
Persistent infection	10 (83.3)	10 (76.9)
Persistent hepatitis E	n=10	n=10
Death before treatment	2 (20.0)	3 (30.0)
Resolved with reduced immunosuppression	1 (10.0)	0
Sustained virological response on ribavirin	4 (40.0)	4 (40.0)
Ribavirin non-responder	2 (20.0)	0
Responsive without sustained virological response	1 (10.0)	3 (30.0)

* Data are presented as No. (%) of participants unless otherwise indicated

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Disclosure

The results of this research have been previously published in:

1. Sridhar S, Yip CCY, Lo KHY, et al. Hepatitis E virus species C infection in humans, Hong Kong. Clin Infect Dis 2022;75:288-96.
2. Sridhar S, Situ J, Cai JP, et al. Multimodal investigation of rat hepatitis E virus antigenicity: implications for infection, diagnostics, and vaccine efficacy. J Hepatol 2021;74:1315-24.
3. Chen Z, Li G, Situ J, et al. Redeveloping antigen detection kits for the diagnosis of rat hepatitis E virus. J Clin Microbiol 2023;61:e0071023.

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