

Increased risk of hepatitis E virus infection in schizophrenia

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Abstract Until now, the risk of HEV infection in schizophrenia was unknown. The present results showed that the seroprevalence of anti-HEV IgG and anti-HEV IgM in schizophrenia were significantly higher than that in healthy controls. Anti-HEV IgG positivity increased with age and with the duration of disease in schizophrenia patients. Moreover, schizophrenia patients with increased CD4⁺/CD8⁺ T-cell ratios (>2.03) had higher anti-HEV IgG detection rates than those with normal ratios (1.05–2.03). Compared with the schizophrenia patients who tested anti-HEV IgG negative, the levels of interleukin-4 and interleukin-10 (Th2 cytokines) were significantly higher, while the interleukin-12 (Th1 cytokine) level was significantly lower, in those with anti-HEV IgG positivity. Of five schizophrenia patients who were anti-HEV IgM positive, four had elevated CD4⁺/CD8⁺ T-cell ratios. HEV RNA was isolated from one of these four patients and classified as genotype 4. Anti-HEV IgM positivity was not detected among healthy controls. Therefore, schizophrenia patients exhibited a higher risk of HEV infection than controls.

Introduction

Hepatitis E virus (HEV) is a non-enveloped, single positive-strand RNA virus in the family *Hepeviridae* with a worldwide distribution [9]. Hepatitis E, caused by HEV, is an important public-health problem in many developing countries and is the cause of sporadic acute hepatitis in developed countries. Although the overall mortality of hepatitis E is less than 1 % in the general population, it can reach up to 19 % in pregnant women in the third trimester [19]. HEV infection has four documented routes of transmission: waterborne, foodborne, bloodborne and vertical transmission from mother to child [1, 2, 12, 33]. Epidemiological studies indicate that a higher prevalence of HEV antibodies is observed in the elderly and people who live in rural areas with poor sanitation [4, 24]. Moreover, isolation of animal strains of HEV and the existence of other animal species that tested seropositive for anti-HEV IgG and IgM indicate that hepatitis E is a zoonotic disease [6, 27].

Schizophrenia is a complex mental disease that is highly heritable, and it involves interplay between genetic and environmental factors. Immune system abnormalities have been reported in patients with schizophrenia, as evidenced by increased expression of proinflammatory cytokines, T-cell activation and high levels of autoantibodies [23]. The alterations of circulating inflammatory cytokines, such as interleukin-2 (IL-2), interleukin-12 (IL-12) and interferon- γ (IFN- γ), reflecting the functions of T help type 1 (Th1), and interleukin-4 (IL-4), interleukin-5 (IL-5) and interleukin-10 (IL-10), reflecting the functions of T help type 2 (Th2), were also observed in previous studies [23, 30]. Moreover, the previous results suggested there was an imbalance between Th1 and Th2 with a shift toward the Th2 system in schizophrenia [30]. Epidemiological studies

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have already shown that the rates of hepatitis B and hepatitis C virus infection in patients with schizophrenia were five and 11 times higher, respectively, than the estimated general population rates [26]. However, the risk of hepatitis E virus infection in schizophrenia is still unknown. In the current study, we found that the detection rates for HEV antibodies in schizophrenia patients were much higher than those in healthy controls. Anti-HEV IgG positivity increased with age and with the duration of schizophrenia. Moreover, schizophrenic patients with increased ratios of CD4⁺/CD8⁺ T cells had higher anti-HEV IgG detection rates than those with normal ratios. Compared with patients who tested anti-HEV IgG negative, the levels of IL-4 and IL-10 were significantly higher, while the IL-12 level was significantly lower in those with anti-HEV IgG positivity.

Material and methods

Study population

This study was carried out between August 2011 and March 2012. Two hundred sixty-nine individuals with schizophrenia (SZ) were enrolled in the present study. The diagnosis of schizophrenia was based on criteria defined by the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision) (DSM-IV TR). The Mini International Neuropsychiatric Interview (MINI) version 6.0.0 DSM was used for screening patients for schizophrenia during data collection. All of the patients who were enrolled were inpatients and were diagnosed by the Department of Psychiatry, Huai'an Third Hospital in Jiangsu, China. Moreover, all of the patients were free of acute infections and allergic reactions for at least two weeks prior to the collection of serum samples.

Two hundred sixty healthy controls (HC) were randomly recruited for age (± 2 years) and gender matching from the annual health examination population (1,608 subjects) living in the same region. All of the healthy controls were found to be free of schizophrenia by screening using the MINI test. Moreover, the inclusion criteria for the healthy controls were the absence of any psychiatric and autoimmune disorders and the lack of a history of these disorders among immediate family members. Additionally, healthy controls had to declare themselves free of acute infections and allergic reactions for at least two weeks prior to the collection of serum samples.

This study conformed to the 1975 Declaration of Helsinki, and it was approved by the Research Ethics Committee of the Huaian Third Hospital, following established guidelines. All participants provided written informed consent after the study procedures were explained.

HEV IgG and IgM antibody detection

Anti-HEV IgG and IgM were assayed using commercial immunoassay ELISA kits (Wantai Biopharmaceutical, Inc., Beijing, China) as described previously [35]. The sensitivity and specificity of the present assays were 97.8 % and 99.9 % for anti-HEV IgG detection, and 96.1 % and 99.4 % for anti-HEV IgM detection, respectively. In brief, plates precoated with recombinant HEV ORF2 proteins were incubated with test sera, as well as reactive and non-reactive controls at 37 °C for 30 min, washed five times and incubated with 100 μ L of human anti-IgG- or anti-IgM-horseradish peroxidase conjugate. After incubation at 37 °C for 30 min, the plates were washed and incubated at room temperature for 15 min with enzyme substrate. Absorbance was read at 492 nm, and the cutoff value was determined according to the manufacturer's instructions.

T-cell subtypes and flow cytometry analysis

Heparinized whole blood (100 μ l) was incubated with anti-CD4 (FITC), anti-CD8 (PE) and anti-CD3 (PerCP) and analyzed by four-color flow cytometry using a fluorescence-activated cell sorter FACSCalibur (Becton-Dickinson, Mountain View, CA) as described elsewhere [34]. A total of 10,000 events were collected in the lymphocyte gate using morphological parameters. Data were processed using CellQuest Pro Software (Becton-Dickinson) and analyzed using the Summit Software. The CD3⁺ T-cell, CD4⁺ T-cell and CD8⁺ T-cell counts were expressed as the proportion of all PBMCs.

Cytokine measurements

The levels of serum IL-4, IL-10, IL-12 and IFN- γ were assayed using commercially available ELISA kits (Yuanxiang Biotech Inc., Shanghai, China). Each cytokine assay was optimized, and a standard curve was established using standard procedures. In brief, plates were precoated with anti-IL-4, anti-IL-10, anti-IL-12 or anti-IFN- γ capture antibody. Plates were washed and incubated with serial dilutions of standards and with test specimens for 2 h at 37 °C. Plates were washed five times, incubated with appropriate biotinylated detection antibody for 2 h at 37 °C, and then washed and incubated for 20 min with streptavidin-conjugated horseradish peroxidase. The reaction was developed with tetramethylbenzidine-H₂O₂ substrate after the final wash. In all assays, the samples were analyzed in duplicate, and the case-control pairs were analyzed on the same plate. The lower limits of detection for IL-4 and IFN- γ were 15 pg/mL, and for IL-10 and IL-12, they were 20 pg/mL, respectively.

HEV RNA isolation, sequencing and analysis

Total RNA from five anti-HEV IgM-positive samples as well as negative and positive controls was extracted from 100 μ L of serum using TRIzol-LS Reagent (Invitrogen, Shanghai, China), reverse-transcribed and subjected to nested PCR to amplify the ORF2 region as described previously [6]. The limit of HEV-RNA detection in the present assay was 1000 copies/mL (5 copies/reaction). After purification using a QIAquick Gel Extraction Kit (QIAGEN, Valencia, CA, USA), the PCR products were sent to Invitrogen and sequenced using an ABI 3130 Genetic Analyzer. Genetic analysis was performed with MEGA Version 4.0 (Tempe, AZ, USA).

Statistical analysis

An unpaired Student's t-test was used to test for differences between SZ and HC groups of continuous variables. Differences in qualitative variables were compared using χ^2 or trend χ^2 tests. A two-sided P-value of <0.05 was set to denote statistical significance. All statistical analysis was performed using Statistical Product and Service Solutions 13.0 (SPSS; SPSS Inc, Chicago, USA).

Results

Demographic, clinical and immune activation characteristics

Demographic and clinical characteristics for patients and controls are shown in Table 1. There were no age or gender differences between schizophrenia patients and controls. Increased levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were detected in 39 and 15 schizophrenia patients, respectively. Six patients had elevated levels of both ALT and AST. In the HC group, only two and eight individuals had elevated levels of ALT and AST, respectively. None of the controls had abnormal levels of both ALT and AST.

In the SZ group, 142 of 269 (52.8 %) patients showed activation of T cells and increased ratios of CD4⁺/CD8⁺ T cells (>2.03), while only eight people in HC group had increased ratios of CD4⁺/CD8⁺ T cells (Table 2). A significant difference was found between the SZ group and the control.

HEV antibody detection in the study population

Correlations between the detection rates, gender and duration of illness are summarized in Table 2. Ninety-four out of 269 (34.9 %) in the SZ group were positive for

anti-HEV IgG, while 70 out of 260 people (26.9 %) in the HC group were positive ($P < 0.05$). Patients with a longer course of disease (>10 years) tended to show higher rates of positivity than did patients with less than 10 years of disease ($P < 0.05$). The detection rates of HEV IgG antibody increased with age in the SZ group but not in the healthy population. There was no significant difference between males and females in either the SZ or the HC group. Additionally, five cases, four males and one female, were HEV IgM antibody positive in the SZ group, but no individuals were anti-HEV IgM positive in the HC group ($P < 0.05$).

Relationship of the ratio of CD4⁺/CD8⁺ T cells to the anti-HEV antibody detection rate

Out of 142 schizophrenia patients with increased CD4⁺/CD8⁺ T cell ratios (>2.03), 72 (50.7 %) were anti-HEV IgG antibody positive, while 22 of the 127 patients (17.3 %) with normal CD4⁺/CD8⁺ T cell ratios (1.05–2.03) were anti-HEV IgG positive ($P < 0.001$) (Table 2). In five cases with anti-HEV IgM antibody positivity, four patients had elevated ratios of CD4⁺/CD8⁺ T cells. There was no difference in anti-HEV IgM antibody detection rates in the patients with or without an elevated ratio of CD4⁺/CD8⁺ T-cells (4/142 vs. 1/127).

Analysis of cytokine levels

The levels of serum IL-12, IFN- γ , IL-4 and IL-10 were measured by ELISA. Significant differences were observed in serum IL-4, IL-10 and IL-12 levels between the schizophrenia patients with higher values of CD4⁺/CD8⁺ T-cell ratios (>2.03) and those with normal values (47.41 ± 6.43 vs. 35.55 ± 6.87 for IL-4, 49.25 ± 7.13 vs. 35.13 ± 6.60 for IL-10 and 29.51 ± 4.32 vs. 39.2 ± 5.80 for IL-12), while no difference in serum IFN- γ level was observed (49.25 ± 7.13 vs. 35.13 ± 6.60 for IFN- γ). In comparison with schizophrenia patients who tested HEV IgG negative, HEV-IgG-positive patients had levels of serum IL-4 and IL-10 that were significantly higher, while the level of serum IL-12 was significantly lower ($P < 0.01$, $P < 0.01$ and $P < 0.01$, respectively) (Table 3). There was no difference in the level of serum IFN- γ between HEV-IgG-positive and negative patients. Moreover, differences in cytokine levels were not observed within the HC group regardless of the HEV IgG status (data not shown).

Analysis of HEV RNA isolated from schizophrenia

Of five anti-HEV-IgM-positive samples, one sample with increased levels of ALT and AST, and an elevated CD4⁺/CD8⁺ T-cell ratio was positive for HEV RNA. The 552-nt

Table 1 Demographic and clinical characteristics of study populations

	SZ (n = 269)	HC (n = 260)	χ^2/t	P-value
Age (years)	38.06 ± 13.11	38.30 ± 13.03	0.205	NS
Gender				
Male	148 (55.0 %)	149 (57.3 %)	0.281	NS
Female	121 (45.0 %)	111 (42.7 %)		
Duration of illness (years)	1-36			
Lab test (normal range)				
ALT (8-40 IU/L)	29.98 ± 36.96	24.08 ± 7.76	2.560	<0.05
AST (8-40 IU/L)	24.22 ± 18.66	19.81 ± 15.68	2.941	<0.01
T cells (normal range)				
CD3 ⁺ T cells (60.8-75.4 %)	76.66 ± 9.75	70.81 ± 7.60	5.466	<0.01
CD4 ⁺ T cells (29.4-45.8 %)	47.68 ± 9.048	39.21 ± 5.66	9.820	<0.01
CD8 ⁺ T cells (18.2-32.8 %)	24.92 ± 3.65	26.00 ± 5.00	2.070	<0.05
CD4 ⁺ /CD8 ⁺ ratio (1.05-2.03)	1.95 ± 4.35	1.56 ± 4.27	6.802	<0.01

Table 2 Anti-HEV IgG detection rates in study populations

	SZ (n = 269)		HC (n = 260)	
	Positive	Negative	Positive	Negative
Total	94 (34.9 %)	175 (65.1 %)	70 (26.9 %)	190 (73.1 %)
P-value	$\chi^2 = 3.977$, P = 0.046			
Gender				
Male	50 (33.8 %)	98 (66.2 %)	43 (28.9 %)	106 (71.1 %)
Female	44 (36.4 %)	77 (63.6 %)	27 (24.3 %)	84 (75.7 %)
P-value	$\chi^2 = 0.195$, P = 0.659		$\chi^2 = 0.665$, P = 0.415	
Duration of illness (years)				
<10 years	47 (29.7 %)	111 (70.3 %)		
≥10 years	47 (42.3 %)	64 (57.7 %)		
P-value	$\chi^2 = 4.550$, P = 0.033			
Age (years)				
15 years-	4 (25.0 %)	12 (75.0 %)	6 (40.0 %)	9 (60.0 %)
20 years-	16 (23.9 %)	51 (76.1 %)	12 (18.5 %)	53 (81.5 %)
30 years-	21 (35.0 %)	39 (65.0 %)	16 (28.1 %)	41 (71.9 %)
40 years-	31 (41.9 %)	43 (58.1 %)	22 (31.0 %)	49 (69.0 %)
50 years-	15 (41.7 %)	21 (58.3 %)	10 (27.8 %)	26 (72.2 %)
60-77 years	7 (43.8 %)	9 (56.2 %)	4 (25.0 %)	12 (75.0 %)
P-value	Trend $\chi^2 = 5.86$, P = 0.015		Trend $\chi^2 = 0.195$, P = 0.659	
CD4 ⁺ /CD8 ⁺				
1.05-2.03	22 (17.3 %)	105 (82.7 %)	68 (27.0 %)	184 (73.0 %)
>2.03	72 (50.7 %)	70 (49.3 %)	2 (25.0 %)	6 (75.0 %)
P-value	$\chi^2 = 32.86$, P < 0.001		$\chi^2 = 0.016$, P = 0.901	

ORF2 sequence of the PCR product was sequenced and compared with those of known HEV isolates. The isolate was 81.9-97.9 %, similar to the genotype 4 isolates, but only 69.5-73.6 %, 69.2 % and 71.2-80.7 %, similar to the

genotype 1, 2 and 3 HEV strains, respectively. Therefore, this HEV isolate, named HEV-HuaiansZ (GenBank no. JX013638) was classified as genotype 4, which was widely distributed in China.

Table 3 Cytokine levels in schizophrenic patients with or without anti-HEV IgG positivity

	Anti-HEV IgG		t	P
	Positive (n = 94)	Negative (n = 175)		
IL-4 (pg/mL)	45.75 ± 7.89	39.70 ± 8.70	5.780	<0.01
IL-10 (pg/mL)	46.85 ± 8.91	40.30 ± 9.59	5.471	<0.01
IFN- γ (pg/mL)	42.93 ± 7.50	41.46 ± 7.98	1.471	NS
IL-12 (pg/mL)	30.78 ± 5.35	35.92 ± 7.19	6.637	<0.01

Discussion

Our study contributes to the sparse literature on HEV seropositivity in schizophrenia patients. In previous studies, higher prevalence of antibodies to HBV nucleocapsid protein was seen in patients with psychiatric disorders [26]. Epidemiological studies also proved that patients with schizophrenia were significantly more likely to be infected with HCV than those without schizophrenia [13, 26]. Moreover, higher seroprevalence of antibodies to cytomegalovirus, herpes simplex virus, human immunodeficiency virus, influenza virus and coronaviruses were found in psychotic patients compared to the general population [3, 8, 18, 21, 25, 28, 29]. Therefore, it was reasonable for us to carry out the present study to evaluate the risk of HEV infection in patients with schizophrenia. The results confirmed our hypothesis that anti-HEV IgG and IgM detection rates in schizophrenia were significantly higher than in healthy controls. Several factors could contribute to higher detection rates of HEV antibody in schizophrenia patients. First, some symptoms of schizophrenia, in particular, the symptoms of cognitive impairment, may contribute directly to an inability to safeguard against the transmission of waterborne, foodborne or bloodborne infection [10]. Second, schizophrenia patients usually reside in settings such as psychiatric facilities, where they often forge social relationships with other higher-risk individuals [8, 25]. Third, financial instability and poverty are also associated with increased risks of HEV infection [4].

The clinical symptoms of hepatitis E are typical of self-limiting, acute viral hepatitis in general [16, 31]. Severe hepatitis E can occur in the elderly, pregnant women and people with chronic hepatitis B and chronic hepatitis C [11, 17, 32]. Chronic hepatitis E infection has also been documented in patients receiving immunosuppressive therapy following organ transplantation and those infected with HIV [15]. The immune responses to HEV involve antibody-mediated immunity, cell-mediated immunity, interferon and other host defenses [5, 7, 14, 22]. Data from cellular immune responses to HEV suggest that the CD8⁺ T-cell count is significantly higher in recovered HEV-

infected individuals than in acutely infected HEV patients and the general population, but the levels of CD4⁺ T-cells are similar in these groups [14, 22, 34]. In schizophrenia, increased levels of CD4⁺ T cells and higher CD4⁺/CD8⁺ T-cell ratios were documented previously [30]. In the present study, the detection rate of anti-HEV IgG in schizophrenia patients with increased CD4⁺/CD8⁺ T-cell ratios (>2.03) was significantly higher than in patients with normal ratios (1.05 ~ 2.03). Thus, further well-designed studies should be carried out to analyze the relationships between CD4⁺/CD8⁺ T-cell levels and the increased risk of HEV infection in schizophrenia patients.

Cellular immune responses to infections can be either of the Th1 type, which is characterized by cytokines such as IL-2, IFN- γ and IL-12, or the Th2 type, which is characterized by cytokines such as IL-4, IL-5, IL-10 and IL-13. In hepatitis B and C virus infections, the predominant immune response, which is Th1, is activated during liver trauma [20]. According to Pal et al. [22], IFN- γ , a Th1 cytokine, was lower in HEV-infected pregnant women than in healthy people. Furthermore, the production of IL-4, a Th2 cytokine, was higher in HEV-infected pregnant women than in controls [22]. These results suggest that pregnant women with acute HEV infection show a shift in the Th1/Th2 balance towards a Th2 response. This shift might play a role in the particularly severe clinical course and mortality of the HEV infection during late pregnancy. It should be noted that schizophrenia might also be associated with an imbalance in Th1/Th2 cytokines, and also with a shift toward the Th2 system [30]. In the present study, the Th2 bias was observed in schizophrenia patients, as evidenced by the increased production of IL-4 and IL-10 and lower IL-12 production. Moreover, significant differences of the serum IL-4, IL-10 and IL-12 levels were observed among schizophrenia patients with and without HEV IgG antibodies.

The major implication of this study is that there may be more potential risk factors in schizophrenia patients, which may be responsible for the increased transmission of HEV. Also, there are several limitations in our present study. First, the various drugs used in schizophrenia may affect the immune system, and virtually all our schizophrenia patients were on this type of medication. Relationships between drugs and immune bias, and the effect of this relationship on the risk of HEV infection in schizophrenia should be assessed in the future. Second, we did not include inflammatory markers other than serum IL-4, IL-10, IL-12 and IFN- γ , and thus, future work should be carefully interpreted in the light of this. Third, larger numbers of schizophrenia patients and controls as well as long-term follow-up will be required to further analyze the increased risk of HEV infection in schizophrenia.

Taken together, schizophrenia patients exhibited higher risk of HEV infection than controls in the present study. Anti-HEV IgG seropositivity increased with age and with the duration of illness. Moreover, schizophrenia patients with increased CD4⁺/CD8⁺ T-cell ratios had higher anti-HEV IgG detection rates than those with normal ratios. The levels of IL-4 and IL-10 were significantly higher, while the IL-12 level was significantly lower in schizophrenia patients with anti-HEV IgG positivity than in those who were antibody negative. In order to understand the questions behind the observed associations, further work is needed, with larger samples and longitudinal follow-ups.

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Conflict of interest The authors declare no conflict of interest.

References

- Aggarwal R, Naik S (2009) Epidemiology of hepatitis E: current status. *J Gastroenterol Hepatol* 24:1484–1493
- Corwin AL, Tien NT, Bounlu K, Winarno J, Putri MP, Laras K et al (1999) The unique riverine ecology of hepatitis E virus transmission in South-East Asia. *Trans R Soc Trop Med Hyg* 93:255–260
- Dickerson F, Stallings C, Origoni A, Copp C, Khushalani S, Yolken Rc (2010) Antibodies to measles in individuals with recent onset psychosis. *Schizophr Res* 119:89–94
- Dong C, Dai X, Shao JS, Hu K, Meng JH (2007) Identification of genetic diversity of hepatitis E virus (HEV) and determination of the seroprevalence of HEV in eastern China. *Arch Virol* 152:739–746
- Dong C, Dai X, Meng JH (2007) The first experimental study on a candidate combined vaccine against hepatitis A and hepatitis E. *Vaccine* 25:1662–1668
- Dong C, Meng J, Dai X, Liang JH, Feagins AR, Meng XJ et al (2011) Restricted enzooticity of hepatitis E virus genotypes 1 to 4 in the United States. *J Clin Microbiol* 49:4164–4172
- Dong C, Zafrullah M, Mixson-Hayden T, Dai X, Liang J, Meng J et al (2012) Suppression of interferon- α signaling by hepatitis E virus. *Hepatology* 55:1324–1332
- Dyer JG, McGuinness TM (2008) Reducing HIV risk among people with serious mental illness. *J Psychosoc Nurs Ment Health Serv* 46:26–34
- Emerson SU, Anderson D, Arankalle VA, Meng XJ, Purdy M, Schlauder GG et al (2004) Hepatitis E virus. In: Fauquet CM, Mayo MA, Maniloff J, Desselberger U, Ball LA (eds) *Virus Taxonomy*, VIIIth Report of the ICTV. Elsevier/Acadmic Press, London, pp 851–855
- Essock SM, Dowden S, Constantine NT, Katz L, Swartz MS, Meador KG et al (2003) Risk factors for HIV, hepatitis B, and hepatitis C among persons with severe mental illness. *Psychiatr Serv* 54:836–841
- Fourquet E, Mansuy JM, Bureau C, Recher C, Vinel JP, Izopet J et al (2010) Severe thrombocytopenia associated with acute autochthonous hepatitis E. *J Clin Virol* 49:141–144
- Hazam RK, Singla R, Kishore J, Singh S, Gupta RK, Kar P (2010) Surveillance of hepatitis E virus in sewage and drinking water in a resettlement colony of Delhi: what has been the experience? *Arch Virol* 155:1227–1233
- Himelhoch S, McCarthy JF, Ganoczy D, Medoff D, Kilbourne A, Goldberg R et al (2009) Understanding associations between serious mental illness and hepatitis C virus among veterans: a national multivariate analysis. *Psychosomatics* 50:30–37
- Husain MM, Aggarwal R, Kumar D, Jameel S, Naik S (2011) Effector T cells immune reactivity among patients with acute hepatitis E. *J Viral Hepat* 18:e603–e608
- Kamar N, Weclawiak H, Guilbeau-Frugier C, Legrand-Abravanel F, Cointault O, Ribes D et al (2012) Hepatitis E virus and the kidney in solid-organ transplant patients. *Transplantation* 93:617–623
- Kamili S (2011) Toward the development of a hepatitis E vaccine. *Virus Res* 16:93–100
- Kc S, Sharma D, Basnet BK, Mishra AK (2009) Effect of acute hepatitis E infection in patients with liver cirrhosis. *JNMA J Nepal Med Assoc* 48:226–229
- Kelly JA, Murphy DA, Sikkema KJ, Somlai AM, Mulry GW, Fernandez MI et al (1995) Predictors of high and low levels of HIV risk behavior among adults with chronic mental illness. *Psychiatr Serv* 46:813–818
- Khuroo MS, Teli MR, Skidmore S, Sofi MA, Khuroo MI (1981) Incidence and severity of viral hepatitis in pregnancy. *Am J Med* 70:252–255
- Nagai H, Miyaki D, Matsui T, Kanayama M, Higami K, Momiyama K (2008) Th1/Th2 balance: an important indicator of efficacy for intra-arterial chemotherapy. *Cancer Chemother Pharmacol* 62:959–963
- Okusaga O, Yolken RH, Langenberg P, Lapidus M, Arling TA, Dickerson FB et al (2011) Association of seropositivity for influenza and coronaviruses with history of mood disorders and suicide attempts. *J Affect Disord* 130:220–225
- Pal R, Aggarwal R, Naik SR, Das V, Das S, Naik S (2005) Immunological alterations in pregnant women with acute hepatitis E. *J Gastroenterol Hepatol* 20:1094–1101
- Potvin S, Stip E, Sepehry AA, Gendron A, Bah R, Kouassi E (2008) Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. *Biol Psychiatry* 63:801–808
- Purcell RH, Emerson SU (2008) Hepatitis E: an emerging awareness of old disease. *J Hepatol* 48:494–503
- Rector NA, Seeman MV (1992) Schizophrenia and AIDS. *Hospital and Community Psychiatry* 43:181–182
- Rosenberg SD, Goodman LA, Osher FC, Swartz MS, Essock SM, Butterfield MI et al (2001) Prevalence of HIV, hepatitis B, and hepatitis C in people with severe mental illness. *Am J Public Health* 91:31–37
- Sato Y, Sato H, Naka K, Furuya S, Tsukiji H, Kitagawa K et al (2011) A nationwide survey of hepatitis E virus (HEV) infection in wild boars in Japan: identification of boar HEV strains of genotypes 3 and 4 and unrecognized genotypes. *Arch Virol* 156:1345–1358
- Severance EG, Dickerson FB, Viscidi RP, Bossis I, Stallings CR, Origoni AE et al (2011) Coronavirus immunoreactivity in individuals with a recent onset of psychotic symptoms. *Schizophr Bull* 37:101–107
- Shirts BH, Prasad KM, Pogue-Geile MF, Dickerson F, Yolken RH, Nimgaonkar VL (2008) Antibodies to cytomegalovirus and Herpes Simplex Virus 1 associated with cognitive function in schizophrenia. *Schizophr Res* 106:268–274
- Suvisaari J, Loo BM, Saarni SE, Haukka J, Perälä J, Saarni SI et al (2011) Inflammation in psychotic disorders: a population-based study. *Psychiatry Res* 189:305–311

31. Tappe D, Müller A, Ziegler U, Weissbrich B, Schubert J, Günther S et al (2010) Positive hepatitis E and Epstein Barr virus serology in a patient with jaundice after travel. *J Clin Virol* 48:78–81
32. Teo CG (2007) The two clinico-epidemiological forms of hepatitis E. *J Viral Hepat* 14:295–297
33. Teshale EH, Howard CM, Grytdal SP, Handzel TR, Barry V, Kamili S et al (2010) Hepatitis E epidemic, Uganda. *Emerg Infect Dis* 16:126–129
34. Tripathy AS, Das R, Rathod SB, Arankalle VA (2012) Cytokine profiles, CTL response and T cell frequencies in the peripheral blood of acute patients and individuals recovered from hepatitis E infection. *PLoS One* 7:e31822
35. Zhu FC, Zhang J, Zhang XF, Zhou C, Wang ZZ, Huang SJ et al (2010) Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial. *Lancet* 376:895–902