# Absence of chronic hepatitis E in a German cohort of common variable immunodeficiency patients

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## Abstract

Cases of chronic or prolonged hepatitis E virus (HEV) infections have been described in solid organ transplant recipients, HIV infected patients and in patients with malignancies or idiopathic CD4+ T lymphopenia. It is unknown if HEV infection also takes chronic courses in patients with common variable immunodeficiency (CVID). We studied a cohort of 73 CVID patients recruited in a low endemic Central European country. None of the subjects tested positive for HEV RNA or anti-HEV IgG. Immunoglobulin transfusions (n=10) tested negative for HEV RNA but all were anti-HEV positive. To verify that such pooled blood products contain anti-HEV protective antibodies we measured the anti-HEV IgG optical density (OD) values in patients before and after transfusion. Anti-HEV OD values increased after infusion but did not reach the cut-off considered as positive. Thus, chronic HEV infections seem to be rare events in CVID patients in Germany. Commercially available immunoglobulin infusions contain anti HEV antibodies and may contribute to protection from HEV infection.

## Introduction

Infections with the hepatitis E virus (HEV) are responsible for outbreaks of acute hepatitis E in many developing countries. In recent years from industrialized countries an increased number of autochthonous cases of hepatitis E has been reported.[1] Of note, hepatitis E may take a severe, chronic course in immunosuppressed individuals, as solid organ transplant recipients as well as in HIV-positive individuals.[2-4] Chronic hepatitis E has also been reported in a patient with idiopathic CD4 lymphocytopenia.[5] However there is currently no data on the incidence and the relevance of HEV infections in patients with common variable immunodeficiency (CVID), a primary antibody deficiency syndrome, which is defined as the triad of recurrent respiratory or gastrointestinal infections, a reduction of immunoglobulin levels and a reduced antibody response to vaccination.[6,7] Some CVID patients may in addition suffer from T cell defects.

CVID patients are treated by intravenous or subcutaneous immunoglobulin replacement therapy or prophylactic antibiotics. Therapy with immunoglobulins increases life expectancy and reduces the frequency and severity of infections.[6,7]

The first aim of this study was to investigate if persistent HEV infections occur in patients with CVID. The second aim of the study was to investigate if immunoglobulin preparations administered to CVID patients contain protective antibodies against HEV.

## Materials and Methods

Seventy-three patients with CVID followed in a special outpatient clinic at Hannover Medical School, Germany, were prospectively screened for HEV RNA and anti-HEV between May 2010 and October 2010. HEV IgG antibody and HEV RNA testing was performed as described previously.[8] The former Abbott Assay, now under distribution by Diasorin/MP Diagnostics was used according to the manufacturer's instruction (MP Biomedicals, formerly Genelabs Diagnostics, Singapore).

All studied CVID patients received immunoglobulins either intravenously, usually every 3-4 weeks, or subcutaneously. The age in this cohort ranged from 19 to 75 years (mean 45 years, SD 15.4), 51% were male (n=37), the ALT values ranged from 11 to 300 IU/L (mean 35 IU/L, SD 37.6), the aspartate aminotransferas values ranged from 15 to 380 IU/L (mean 38 IU/L, SD 43.2). In 4 of the patients an additional T-cell defect has previously been diagnosed. Statistical analysis was performed using chi-square test. A $P<0.05$ was considered significant. The study was approved by the ethics review board of Hannover Medical School. Written consent was obtained from the participating patients.

To investigate if immunoglobulin infusions contain protective anti HEV antibodies or HEV RNA we tested 10 of pooled blood products for HEV-RNA and anti-HEV IgG.

In addition we took blood from 4 CVID patients directly before transfusion of immunoglobulins and half an hour after the infusion was stopped. This blood was tested for anti HEV IgG to determine the change of the OD-value of the enzyme-linked immunosorbent assay (ELISA) as a marker of the increase of anti-HEV specific immunoglobulins.

## Results

In 23 of the 73 CVID patients (32%) ALT levels were elevated at the time of HEV testing. There was no evidence for concomitant HBV or HCV infections. Of note, none of the CVID patients tested positive for HEV-RNA or anti-HEV IgG. None of the 10 examined immunoglobulin preparations contained detectable HEV RNA. All products tested positive for anti HEV IgG. In four patients we measured anti HEV IgG OD value directly before transfusion of immunoglobulins and 30 min after the infusion. The OD value increased in all patients and even doubled in two of the four subjects. However, OD values did not reach the level of 0.5 which has been defined by the manufacturer as the cut-off for positive results.

## Discussion

The present study shows a lack of chronic HEV infections in CVID patients in a non-endemic country. This finding is in contrast to the increasing number of studies demonstrating persistent HEV viremia in other cohorts of immunocompromised individuals such as solid

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Key words: hepatitis E, common variable immunodeficiency

Conflict of interest: the authors report no conflicts of interest.

Aknowledgments: the authors would like to thank Dr. Horn-Wichmann for his contribution as the first author.

Received for publication: 10 October 2011.
Revision received: 4 March 2012.
Accepted for publication: 10 March 2012.


*Infectious Disease Reports 2012; 4:e28*
*doi:10.4081/idr.2012.e28*

organ transplant recipients, HIV-infected individuals and also single patients with T cell deficiency.[2] The CVID patients included in this study received intravenous immunoglobulins on a regular basis which could have contributed to prevention of HEV infections. Indeed, antibodies against HEV were found to be present in the immunoglobulin preparations by ELISA. The results might be misleading as an ELISA frequently gets falsely positive due to very high immunoglobulin concentrations in the preparations. However, anti HEV OD values measured shortly after the immunoglobulin infusions increased slightly suggesting that the preparations might indeed contain anti HEV immunoglobulins even though the ODs did not reach the pre-defined cut-off for positive results. It can not be ruled out, that the increase of the OD-value is founded in unspecific bindings of the diagnostic ELISA with various transfused immunoglobulins. Therefore this result should not be overestimated.

The specific underlying immunological disorder in the CVID cohort is also heterogeneous and some subjects may still have functional cellular immune responses. We recently gained evidence that HEV-specific T cell responses can contribute to the control of HEV infection[9] and thus T cells in the absence of antibodies may also have contributed to the absence of HEV infections in this cohort. The importance of T cells for clearance of HEV is highlighted by a case report of chronic hepatitis E in a patient with idiopathic $CD4^+$ T cell lymphocytopenia.[5] The present study focussed on CVID patients with a lack of adequate immunoglobulins and only 4 patients with an additional T-cell defect were included. Additional studies should systematically examine the frequency of chronic HEV infections in patients with a disturbance of their cellular immunity. Even though there was no case of chronic HEV infection in the studied cohort, we still would suggest testing immune compromised patients with biochemical signs of hepatitis for HEV RNA. Chronic hepatitis E may take clinical severe courses leading to progressive liver disease and even hepatic failure[2] and thus diagnosis of HEV infections should not be missed. Prevention of HEV infection by vaccination is still not possible even though a successful phase 3 study has recently been published.[10] It needs to be determined whether this vaccine will also be effective in immunosuppressed patients including CVID patients.

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