

Hepatitis E virus-induced severe myositis

To the Editor:

Genotype 3 hepatitis E virus (HEV3) infection is responsible for self-limiting acute hepatitis, chronic HEV3 infection leading to cirrhosis in immunosuppressed patients, and several extra-hepatic manifestations, i.e., neurological symptoms, kidney injury, and severe thrombocytopenia [1–5]. Ribavirin therapy has been shown to be an efficient therapy for chronic HEV infection [6,7]. Herein, we report on a first case of Guillain-Barré syndrome associated with severe necrotizing myositis that occurred in a liver-transplant patient in acute HEV-infection phase, who then recovered after ribavirin therapy.

A 65-year-old liver-transplant male presented, 7 years after transplantation for alcoholic liver disease, with an autochthonous acute HEV infection (Fig. 1): jaundice, increased liver-enzyme levels, positive serum HEV RNA (126,000 copies/ml, genotype 3f), and positive anti-HEV IgG and IgM (Wantai Biologic Pharmacy Enterprise, Beijing, People's Republic of China). All other causes of hepatitis were ruled out. The source of HEV infection has not been clearly identified. However, the patient had eaten undercooked pork meat. He was receiving cyclosporine A (C2 level at 600 ng/ml), mycophenolatemofetil, and steroids. Cyclosporine A doses were dramatically decreased (C2 level at 300 ng/ml). Ten days later, he was unable to stand upright.

Neurological examination showed severe quadriparesis, with proximal muscle weakness and abolition of biceps, patellar, and Achilles' tendon reflexes, as well as a right lower facial palsy. Creatine kinase (CK) level was increased to 191,603 IU/L (normal <170 IU/L). Electrophysiological studies showed signs of peripheral demyelinating polyradiculopathy with abolition or prolongation of F-wave responses and sensory conduction was altered more in upper limbs. At rest, needle electromyography showed diffuse abnormal spontaneous activity in all four limbs. Cerebrospinal-fluid (CSF) analysis showed elevated protein level (0.64 g/L), no leukocytes, and no HEV RNA, whereas serum HEV RNA was still positive (49,600 copies/ml). The CSF to serum-albumin ratio was 12.81. The CSF (IgG:albumin) ratio was 0.47. Cryoglobulinemia, serum anti-ganglioside (GM1, GM-2, GM-3, GM4, GD1A, GD1B, GD2, GD3, GT1A, GD1B, GQ1B) antibodies, anti-myelin-associated glycoprotein antibodies, as well as serum and CSF onconeurological antibodies, were negative. A biopsy specimen of the left bicep brachial muscle showed myopathic changes, with a significant percentage of necrotic muscle fibers ($\approx 10\%$) and some inflammatory elements. There was no capillary thickening.

The day after admission, he developed acute respiratory failure that required mechanical ventilation. Because of suspected HEV-induced Guillain-Barré syndrome associated with severe myositis, mycophenolatemofetil was withdrawn and the patient was given intravenous immunoglobulins (1 g/kg/d for 2 days) and ribavirin therapy [400 mg/d adapted to his glo-

merular filtration rate (40 ml/min)]. Rapidly after the initiation of both therapies, CK and ALT levels decreased and returned to within the normal range, respectively, 3 and 30 days later. Serum HEV RNA became undetectable by day 15, but ribavirin therapy was continued for 3 months as initially scheduled. Two months after ribavirin was stopped, serum HEV RNA was still negative. Fifteen days after HEV clearance, progressive recovery of mobility was noted.

An electromyograph, performed at 2 months after initiation of ribavirin treatment, i.e., 1.5 months after HEV clearance, showed myopathic changes to weak muscles. Studies on nerve conduction showed stable demyelination and severe sensitive-motor axonal injury. Unfortunately, due to mechanical ventilation, he developed a pulmonary infection that evolved to septic shock, which was complicated by ischemic necrosis of the cecum. Currently, he continues rehabilitation and is being weaned off mechanical ventilation.

HEV-induced Guillain-Barré has been previously reported [3]. However, this is the first case of HEV-induced severe myositis. Similar to HCV-induced myositis [8], in the present case, Guillain-Barré syndrome and severe myositis seem to be related to an auto-immune response. Interestingly, the use of ribavirin allowed rapid clearance of HEV infection, which may have accelerated the neurological and muscle recovery.

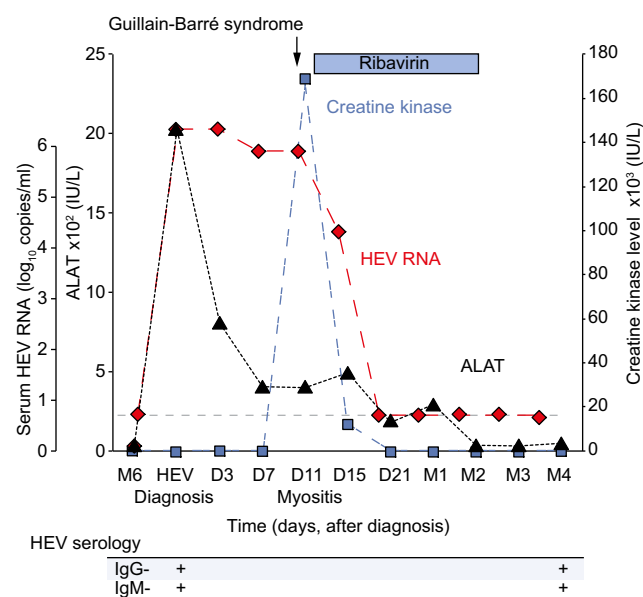


Fig. 1. Outcome of biochemical and virological parameters.



Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Impact of subclinical hypothyroidism on the development of non-alcoholic fatty liver disease: A prospective case-control study

To the Editor:

We read with great interest the article by Chung *et al.* [1] showing that subclinical hypothyroidism, even in the range of upper normal thyroid stimulating hormone (TSH) levels, was closely associated with non-alcoholic fatty liver disease (NAFLD) in a dose-dependent manner. Their results indeed provided important evidence, confirming the close relationship between these two diseases. However, as mentioned by the authors, the causal relationship between hypothyroidism and NAFLD could not be identified by their cross-sectional study.

Recently, we have performed a prospective case-control study to evaluate the impact of subclinical hypothyroidism on the development of NAFLD in a Chinese population. The study was conducted among the employees of Zhenhai Refining & Chemical Company Ltd., Ningbo, China, since 2006. The study population was described in detail in our previous studies [2,3]. A total of 327 subclinical hypothyroidism subjects were enrolled. Age, gender, and body mass index (BMI) are three major factors that may influence the development of NAFLD. To reduce the influence of these variables, we randomly selected 327 age, gender, and BMI matched euthyroid subjects as controls.

All the subjects were free of NAFLD at baseline, and did not have a history of excessive alcohol consumption or liver disease. Subclinical hypothyroidism was defined as a TSH level of 4.5 mIU/L or greater, after excluding subjects with an abnormal thyroxine level [4,5]. NAFLD was diagnosed based on the results of abdominal ultrasonography, after exclusion of alcohol consumption, viral, or autoimmune liver disease [6,7]. The development of NAFLD was evaluated annually during follow-up by ultrasound examination, using a Toshiba Nemio 20 sonography

machine with a 3.5-MHz probe (Toshiba, Tokyo, Japan). Ultra-sound studies were carried out by experienced ultrasonographers who were blinded to the clinical and laboratory data.

A total of 63 subclinical hypothyroidism subjects and 35 euthyroid subjects developed NAFLD during a median follow-up of 4.92 years. Compared to the euthyroid subjects, the incidence of NAFLD for 1000 person-years of follow-up was significantly higher in the subjects with subclinical hypothyroidism (38.3 vs. 21.8; $p < 0.05$).

Subclinical hypothyroidism subjects were further classified into three subgroups according to their TSH levels: 4.5–6.9 mIU/L (mild elevation), 7.0–9.9 mIU/L (moderate elevation), and 10.0 mIU/L or greater (severe elevation). The incidence of NAFLD showed an increased trend with increasing TSH levels. The incidence of NAFLD per 1000 person-years of follow-up was 21.8, 34.2, 48.3 and 52.5 for the euthyroid, mild, moderate and severe elevation subgroup, respectively ($p < 0.05$ for trend). This observation indicated that subjects with higher baseline TSH levels are more likely to develop NAFLD during the follow-up period.

Cox proportional hazards regression analyses were used to estimate hazard ratios for incident NAFLD for subclinical hypothyroidism over the follow-up period. Our analysis showed that subclinical hypothyroidism was a risk factor for the development of NAFLD in the unadjusted model, the hazard ratio (95% CI) was 1.77 (1.17–2.67). The metabolic syndrome is a major mediating variable for the studied relationship. Therefore, we further adjusted the indicators of the metabolic syndrome in the Cox proportional hazards regression analysis. Our result showed that the relationship of subclinical hypothyroidism with incident NAFLD