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Abstract

The use of direct antiviral agents (DAAs) for hepatitis C virus has led to a paradigm shift from viral hepatitis to non-viral disease. Autoimmune hepatitis (AIH) remains to be an issue in liver disease after the DAAs era. Moreover, fatty liver had been increasing in incidence and has attracted attention because of its risk for hepatocellular carcinoma. In 2011, the Great East Japan Earthquake, with the associated tsunami and accident at Fukushima Daiichi Nuclear Power Plant, has changed the lifestyle of residents in Fukushima prefecture. In this manuscript, we outlined the recent topics about AIH, fatty liver, and Fukushima.

Key words : autoimmune hepatitis, non-alcoholic fatty liver disease, the Great East Japan Earthquake, the Fukushima Heath Management Survey

1. Autoimmune Hepatitis

Although the true causes of autoimmune hepatitis (AIH) have not been elucidated, various immune systems had been associated with it[1]. Prednisolone (PSL) is first-line treatment of AIH[2,3], but AIH can relapse during both withdrawal and administration of PSL. In addition to chronic hepatitis or cirrhosis, acute hepatitis had been gradually known as one of the features of AIH[2]. In this chapter, we reviewed the relapse and acute hepatitis in AIH.

1-1 Relapse of AIH

AIH patients frequently relapse after discontinuation of therapy[4]. Among AIH patients, cirrhosis and esophageal varices or hepatic failure had been shown to develop more often in patients with relapse than in those without relapse[5,6]. Moreover, repeated relapse is associated with poor prognosis[7]. Disease activity is the main reason for AIH relapse. The histologic resolution of interface hepatitis or portal plasma cell infiltration had been shown to decrease the chances for relapse after withdrawal of corticosteroids[5]. Normal laboratory findings, such as aminotransferase, globulin, and immunoglobulin G (IgG), had also been associated with relatively low relapse rate[8,9]. In addition, an international AIH group score of ≥17 had been associated with relapse[10].

The factors associated with treatment had been strongly associated with AIH relapse ; these include the duration until treatment cessation[11] ; young age at the time of drug withdrawal ; and combination therapy of corticosteroids and azathioprine[12]. The first-line therapy for AIH is corticosteroid, which is gradually tapered along with AIH improvement[2,3]. Although the guidelines on AIH treatment had proposed a schedule for corticosteroid tapering[3], the effects of dose reduction or rate of taper on AIH relapse have not been elucidated. We previously reported that tapering of corticosteroid until normalization of alanine aminotransferase was a risk factor for AIH relapse[13]. Taken together, accurate evaluation of disease activity and its corresponding treatment is essential to prevent AIH relapse.

1-2 Acute hepatitis of AIH

AIH had been considered to be a chronic liver disease. On the other hand, some patients can have atypical features, including acute presentation. A recent nationwide survey in Japan revealed that the prevalence of chronic hepatitis, acute hepa-

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titis, and cirrhosis was 79.6%, 11.7%, and 6.7%, respectively[14]. AIH with acute presentation is classified into two types : 1) the acute exacerbation phase, in which patients present with the clinical features of acute hepatitis, with histologic evidence of chronic hepatitis and 2) the acute hepatitis phase, in which patients present with histologic features of acute hepatitis[15]. A recent study reported that the prominent presence of lobular and perivenular necroinflammatory activity, pigmented macrophages, and cobblestone appearance of hepatocytes, in addition to plasma cell infiltration and emperipolesis, were useful for the pathologic diagnosis of the acute presentation of AIH[16]. However, an accurate differentiation between the two types of AIH with acute presentation may be difficult, when based on histologic findings alone[17].

The acute presentation of AIH has a varied clinical course, such as acute hepatitis, severe hepatitis, or acute liver failure[18]. A recent Japanese AIH nationwide survey showed the characteristics of 1,682 AIH patients with acute hepatitis and chronic hepatitis[14]. Compared with patients with chronic hepatitis, those with acute hepatitis had significantly higher serum levels of aspartate aminotransferase, alanine aminotransferase (ALT), alkaline phosphatase, and total bilirubin upon diagnosis and significantly lower serum IgG and antinuclear antibody (ANA) titers.

Regarding treatment, the initial dose of PSL and the frequency of steroid pulse therapy were higher in patients with acute hepatitis than in those with chronic hepatitis in Japan[14,18]. A recent study reported the efficacy of high-dose intravenous corticosteroids on AIH patients with acute severe hepatitis[19]. The reported relapse rate of AIH with acute presentation was 29.4%, which was not significantly different from that of AIH with chronic hepatitis[14]. Although the prognosis of AIH with acute hepatitis have not been elucidated, prompt treatment may improve the prognosis, regardless of disease severity.

2. Fatty liver

The liver is a representative organ of ectopic fat ; therefore, obesity is a major cause of fatty liver. Unhealthy lifestyle causes obesity, which results to fatty liver. Non-alcoholic fatty liver disease (NAFLD) had become widespread worldwide, along with the increasing incidence of obesity. NAFLD ranges from simple steatosis to non-alcoholic steatohepatitis (NASH), which has the potential to progress to hepatocellular carcinoma. Various mechanisms mediate fatty liver progression to NASH and had been collectively called as "multiple hit"[20]. The differences in the hit points may explain the difficulty of NAFLD treatment. Weight loss by diet modification or exercise is the gold standard of NAFLD treatment, but it is difficult to achieve. The key lifestyle interventions now include new aspects, such as cognition and sleep.

NASH is diagnosed based on histologic findings of the liver, because there is no disease-specific marker. However, it may be difficult to differentiate between NASH and AIH[21]. In this chapter, we described exercise therapy for NAFLD and new NAFLD topics, such as cognition and sleep. Moreover, we discussed the differentiation between NASH and AIH.

2-1 Exercise therapy for NAFLD

Exercise therapies are generally classified as aerobic or resistance. A recent meta-analysis reported that resistance exercise was more feasible than aerobic exercise for NAFLD patients with poor cardiorespiratory function[22]. Resistance exercise comprises many methods to train the muscles and generally needs training equipment ; these factors can be a weak point when performing the resistance exercise. To overcome this weak point, we proposed a simple non-equipment resistance exercises, such as push-ups and squats, for patients with NAFLD and found that performance of these simple exercises for 12 weeks decreased liver fat and improved insulin resistance[23]. In addition, the patients in that study could perform the exercises, regardless of the background characteristics, such as age, sex, and metabolic complications. Furthermore, we demonstrated that, in patients with NAFLD, performance of those exercises for 24 weeks improved the serum ALT levels[24]. Exercise is a promising approach to overcome NAFLD ; therefore, selection of an exercise that is appropriate for each patient is important.

2-2 Effects of cognition and sleep on NAFLD

Excess food intake or less physical activity can cause NAFLD ; therefore, lifestyle intervention is the basic treatment for patients with NAFLD. Cognition for lifestyle may be important to prevent and improve NAFLD. In fact, cognitive behavioral therapy had been shown to be useful[25], and one epidemiologic study revealed a decline in cognition in patients with NAFLD[26]. Moreover, we previously reported reduced brain activity, as measured by near-infrared spectroscopy, in female patients with NAFLD[27].

Obstructive sleep apnea syndrome is the most famous sleep disorder in NAFLD[28]. In addition, short sleep duration has recently gained attention as a risk for NAFLD[29]. We previously reported that sleep shortage was associated with NAFLD in women[30]. Accordingly, improvement of sleep conditions can be a new strategy for the treatment of NAFLD.

2-3 NAFLD and AIH

Patients with NAFLD are sometimes positive for ANA[21], which is a diagnostic criterion for AIH. Liver histologic findings are the gold standard for the diagnosis of NASH and AIH. On the other hand, the pathologic features of both NASH and AIH can sometimes overlap[21]. In particular, the three types of NASH-AIH overlap include 1) AIH onset after dyslipidemia treatment in patients with NASH, because statins are associated with AIH ; 2) NASH onset after corticosteroid therapy for AIH ; and 3) simultaneous development of NASH and AIH in the absence of drugs. The treatment for patients with NASH-AIH overlap is difficult, because corticosteroids can cause NASH. In fact, a consensus on the therapy for NASH-AIH overlap has not been established.

A cohort study initially demonstrated that patients with AIH and coincident NAFLD were more likely to present with cirrhosis and to develop adverse clinical outcomes, with decreased survival[31]. We recently reported on NAFLD in patients with AIH, based on a nationwide survey in Japan in 2015[32] and found that compared with patients with AIH without NAFLD, those with AIH with NAFLD had lower female-to-male ratio ; older age ; mild elevation in hepatobiliary enzymes ; histologically progressive fibrosis and mild plasma cell infiltration or mild lobular hepatitis ; lower prevalence of PSL administration and higher prevalence of ursodeoxycholic acid administration ; higher levels of hepatic enzymes and IgG after treatment ; and similar prevalence of autoimmune and malignant complications. Understanding these differences is important for the proper diagnosis and treatment of AIH patients with NAFLD.

3. Fukushima

Fukushima faced the triple disaster, including the Great East Japan Earthquake, tsunami, and the Fukushima Daiichi Nuclear Power Plant accident, in March 2011. More than 160,000 residents evacuated away from their hometowns, which were the designated areas for evacuation, near the Fukushima Daiichi Nuclear Power Plant. The Fukushima Heath Management Survey (FHMS) was built to monitor the long-term health of residents in this area[33]. Various health problems following the disaster had been reported from the Comprehensive Health Check of the FHMS[34-41]. In this chapter, we presented our reports on the hepatobiliary enzyme abnormalities after the triple disaster[42-44].

3-1 Hepatobiliary enzymes abnormalities before and after the disaster

A longitudinal survey of 26,006 Japanese men and women living near the Fukushima Daiichi Nuclear Power Plant was undertaken, using data before and after the disaster, with a mean follow-up of 1.6 years[42]. In all participants, the prevalence of hepatobiliary enzyme abnormality (HEA) significantly increased from 16.4% before the disaster to 19.2% after the disaster. The incidence of HEA was significantly higher in evacuees than in non-evacuees. Multivariate logistic regression analysis showed that evacuation was significantly associated with HEA among the residents.

3-2 Effects of lifestyle on hepatobiliary enzyme abnormalities following the disaster

A cross-sectional study was aimed to evaluate the associations of HEA with specific lifestyle factors among 22,246 residents, based on Comprehensive Health Check and the Mental Health and Lifestyle Survey from June 2011 to March 2012[43]. Residents were divided into 2 groups (i.e., evacuee and non-evacuee), based on housing status and residential area after the accident. HEA was present in 27.3% of subjects and has a significantly higher prevalence in evacuees than in non-evacuees (29.5% vs. 25.7%, $P < 0.001$). Multivariate logistic regression analysis revealed that age, sex, moderate to heavy drinking, and low/no physical activity were significantly associated with HEA, regardless of the evacuation status. Unemployment and changes in jobs were significantly associated with HEA in evacuees and non-evacuees, respectively.

3-3 Trends in hepatobiliary enzyme abnormalities after the disaster

A longitudinal survey that enrolled 20,395 adults living in the vicinity of Fukushima Daiichi Nuclear Power Plant was aimed to determine the long-term trends in HEA[44]. In addition to the trends in HEA, the associations of lifestyle factors with the changes in HEA, immediately and 3-4 years after

the disaster, were assessed. Over the study period, the prevalence of HEA significantly decreased from 29.9% to 27.1%. Multivariate logistic regression analysis revealed significant associations of improved HEA with improvements in daily physical activity and frequency of breakfast consumption.

Conclusion

Although the 3 topics of AIH, fatty liver, and Fukushima disaster may seem independent, these had some overlaps and connections, which may evoke new clinical questions for researchers and clinicians.

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Conflict of interest

The authors have no conflict of interest.

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