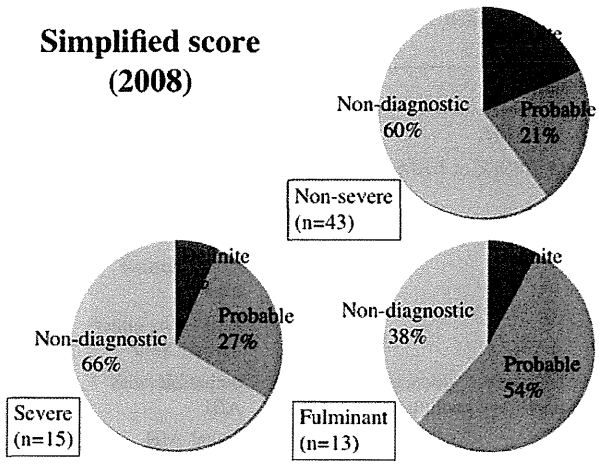

Fig. 7 Discrimination of acute onset AIH patients using the simplified scoring system

pattern of CK19 staining showed a lower intensity with fewer visualized cells than those of CK7, and CK19 was positive in transitional cells in the bile ductular lineage and bile duct cells and negative in progenitor cells, transitional cells in hepatocytic lineage, and hepatocytes; therefore, CK7 is superior to CK19, as a marker of liver regeneration.

Bile ductular reactions consist of bile ductules with poorly defined lumina located at the portal parenchymal interface, arranged in anastomosing cords, and lined with small cells with little cytoplasm, and show strong homogeneous cytoplasmic and membranous CK7-staining patterns. PCs are isolated small cells and show a strong homogeneous cytoplasmic and membranous staining pattern located distal to the bile ductular reactions and occasionally in the sinusoids. Intermediate hepatocytes are defined as cells intermediate in size with histochemical staining between progenitor cells and hepatocytes, and show a variable cytoplasmic and membranous staining pattern in the periportal areas and occasionally with extension into the lobular areas [46].

In our analyses of acute onset AIH patients by CK7 staining, more intermediate hepatocytes and intralobular PCs were found in nonsevere and recovered AIH patients, suggesting that liver regeneration was not impaired in these patients. On the other hand, the marked formation of bile ductules was found in periportal areas, but intermediate hepatocytes and PCs were not seen in fulminant and dead cases, suggesting that liver regeneration was impaired [47]. We suggest that the differentiation from periportal PC to intermediate and mature hepatocytes is maintained in

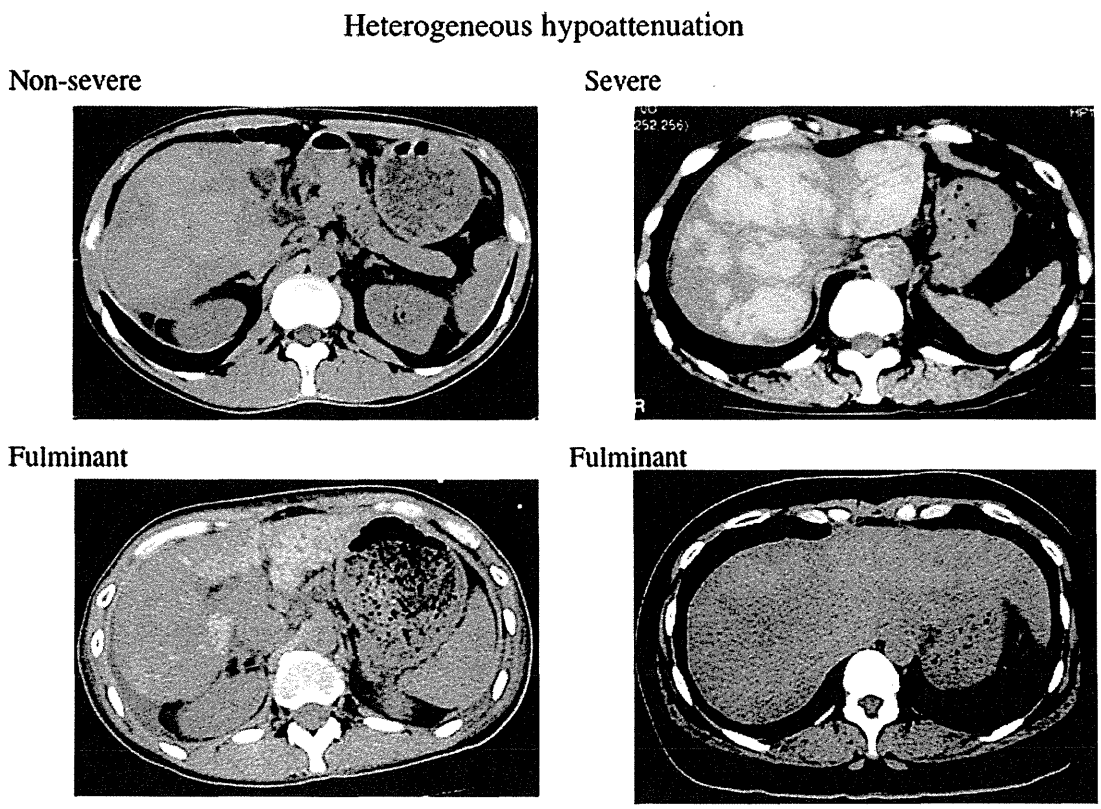

Fig. 8 Heterogeneous hypoattenuation pattern on unenhanced CT in acute onset AIH. Patients with autoimmune ALF often show a variety of heterogeneous hypoattenuation

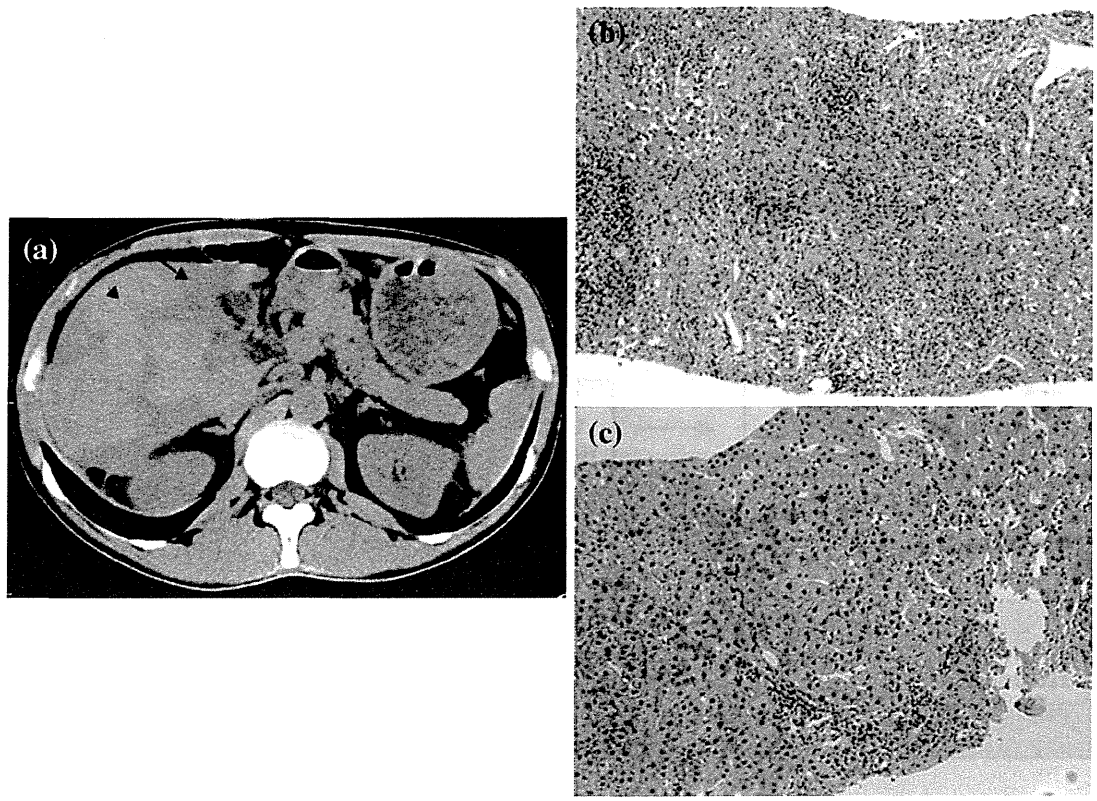

Fig. 9 CT and histological findings of a 43-year-old male patient with nonsevere AIH. **a** CT scan showed heterogeneous hypoattenuating areas. **b** Liver histology showed massive necrosis with plasma cell accumulation in a hypoattenuating area (*arrow area*), and **c** liver regeneration in a nonhypoattenuating area (*arrow head area*)

Table 4 Imaging findings of patients with autoimmune and viral acute liver failure

	Autoimmune ALF	Viral ALF	*p* value
n	23	45	
CT findings			
Hypoattenuation	15	23	0.198[a]
Diffuse	0	22	
Heterogeneous	15	1	0.001[a]

ALF Acute liver failure, *CT* computed tomography

[a] Fisher's exact probability test

nonsevere cases and survivors, but it is impaired in fulminant cases and nonsurvivors, resulting in the marked formation of bile ductules and resistance to immunosuppressive therapy (Fig. 11).

Therapy for acute onset AIH

Nonsevere acute onset AIH patients respond well to corticosteroid (CS) therapy as well as chronic ones. For patients presenting with autoimmune ALF, liver transplantation is indicated by the American Association of the Study of Liver Diseases (AASLD) practice guideline 2010 [48]. Czaja et al. [49] reported that CSs are effective in 36–100 % of cases in acute severe AIH, and suggested that MELD score of $\geq$12 would identify 97 % of treatment failures. The mean MELD score at admission of our fulminant patients was 26.3 ± 6.6 (18–37), and that of our severe patients was 18.5 ± 7.9 (10–42) [37]. They also suggested that failure to improve at least one laboratory abnormality reflective of liver inflammation or function, especially a pretreatment hyperbilirubinemia, within 2 weeks, indicates the need of emergency liver transplantation, and that protracted immunosuppressive therapy can be complicated by infection [49].

In our experience, the improvement in the PT activity, a marker of liver regeneration, during the first 2 weeks after the CS treatment was statistically significant in responders, but not in nonresponders. Even in the responders, the improvement in the liver function, especially T-BIL, was slow in our patients [31]. On the other hand, the mean duration between the introduction of CSs and the onset of sepsis was 14.8 ± 9.7 days in our fulminant AIH patients. Therefore, we also suggest that 2 weeks after the administration of immunosuppressive therapy is indeed a critical

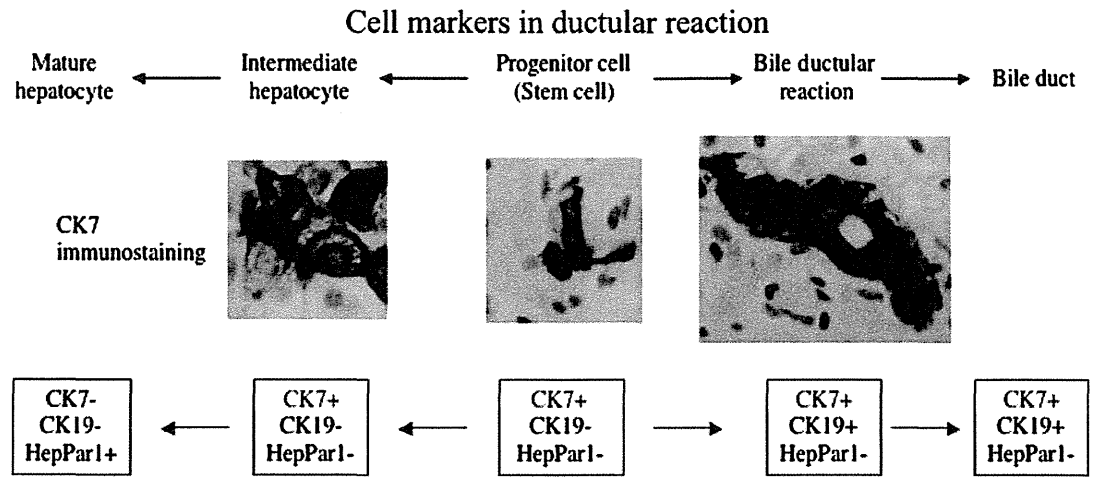

Fig. 10 Cell markers in ductular reaction. Single progenitor cells, intermediate hepatocytes, and ductular reactions could be stained with CK7, and they could be distinguished by morphologic characteristics. *CK* cytokeratin

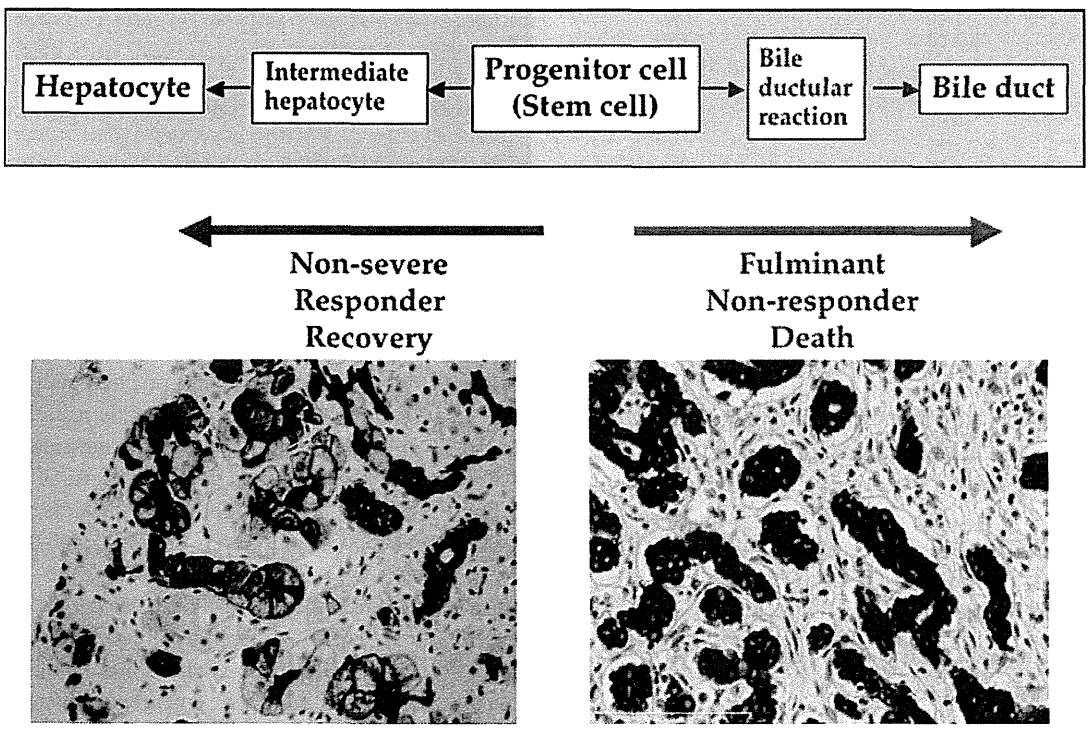

Fig. 11 Liver regeneration and clinical severity in acute onset AIH. The differentiation from periportal progenitor cell to intermediate and mature hepatocytes is maintained in nonsevere cases and survivors, but it is impaired in fulminant cases and nonsurvivors, resulting in the marked formation of bile ductules and resistance to immunosuppressive therapy

point for avoiding infectious complications and switching to liver transplantation.

On the other hand, Ichai et al. [50] reported that CS therapy is ineffective in most of severe and fulminant AIH cases and that it may favor septic complications, and concluded that such patients should be referred for liver transplantation as soon as possible. The treatment decision against CS therapy in autoimmune ALF is difficult especially in Japan where the problems of a shortage of donor livers exist. Czaja claimed that the error to avoid treatment in patients who might respond but otherwise die is greater than that to introduce therapy to patients who will not improve and may worsen, until there are more reliable indices of prognosis than are currently available [51].

Multiple immunosuppressive agents including cyclosporine, tacrolimus, mycophenolate mofetil, budesonide, etc., have emerged and been used empirically as salvage therapies, but their efficacies in autoimmune ALF has not been established yet.

Glycyrrhizin, an aqueous extract of licorice root, has been used for more than 50 years in Japan as a treatment for various liver diseases, mainly chronic viral hepatitis. Intravenous glycyrrhizin significantly lowered ALT and improved liver histology in chronic active hepatitis. Recently, we showed that we could control the ALT level at an early stage of acute onset AIH by a sufficient dose of intravenous glycyrrhizin without a significant difference compared to combination therapy with intravenous glycyrrhizin and corticosteroid, and with a significant difference compared to historical controls [52]. Intravenous glycyrrhizin can also be used safely and has a favorable effect on patients with acute liver disease difficult to diagnose and treat, like cryptogenic hepatitis and acute onset AIH, as an "initial" treatment tool to improve liver inflammation before diagnosing the disease and starting disease-specific treatments. It is obvious that the main treatment strategy for AIH is early immunosuppression.

Summary

The diagnosis of acute onset AIH has been difficult in those patients who show acute presentation like acute hepatitis and may not have typical clinicopathological features of AIH. Therefore, patients with acute onset AIH are at risk of losing the timing of starting immunosuppressive therapy; some of them develop the severe or fulminant form in the "subacute" clinical course, and are sometimes resistant to immunosuppressive therapy and have poor prognosis.

For early diagnosis, we should exclude other causes systematically, remember acute onset AIH in the differential diagnosis, and then apply the revised original scoring system (1999), and comprehensive evaluations of clinical, biochemical, radiological, and histological features are necessary. Especially, precise histological evaluation (presence of "centrilobular necrosis/collapse") plays an important role in the differential diagnosis.

The pathological characteristic of acute onset AIH is its "heterogeneity," especially in ALF. Histological heterogeneity leads to radiological and clinical heterogeneity. Unenhanced CT often shows heterogeneous hypoattenuations reflecting histological massive hepatic necrosis. This finding could be one of the tools for diagnosing autoimmune ALF in combination with the international AIH scoring system. Characteristic morphological patterns of liver necrosis and regeneration would exist in acute onset AIH and their better understanding would be of help for the diagnosis and treatment.

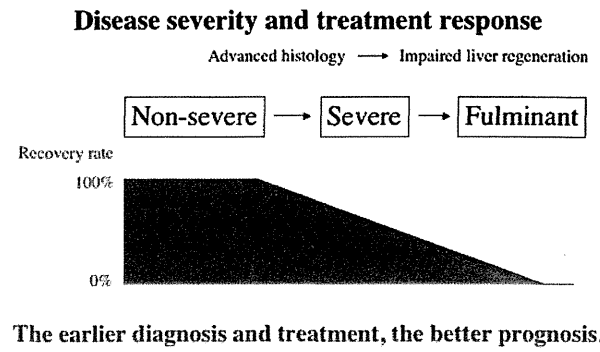

Fig. 12 Disease severity and treatment response in acute onset AIH

For the treatment of autoimmune ALF, liver transplantation should be considered before the occurrence of infectious complications, especially in the case of fulminant liver failure. The most important treatment strategy is to diagnose and treat acute onset AIH before its development into ALF (Fig. 12).

Acknowledgements We are indebted to all our colleagues at the Liver Unit of our hospital who cared for the patients described herein. This study was supported in part by a Health Labour Sciences Research grant from the Ministry of Health, Labor and Welfare of Japan as a project by the Intractable Hepatobiliary Disease Study Group of Japan.

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Letters to the Editors

Letter: treatment of autoimmune acute liver failure – beyond consensus guidelines

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doi:10.1111/apt.12480

SIRS, We read with great interest and agreement the review article by Czaja [1] who reported the management of autoimmune hepatitis (AIH) beyond consensus guidelines. As he described in the review, 'highly individualised clinical judgments are required at decision points that are outside confident guidelines, and these judgments can be difficult and controversial'.

The aetiology of fulminant hepatitis in our unit was due to AIH in 29.3%, after the establishment of the international AIH criteria.[2] In a recent Japanese nationwide survey, the number of patients with AIH showing the histological features of acute hepatitis, including acute liver failure (ALF), has been increasing.[3] The US ALF Study Group reported that 58% of indeterminate ALF were considered autoimmune ALF.[4] Therefore, AIH is a major aetiology of ALF worldwide.

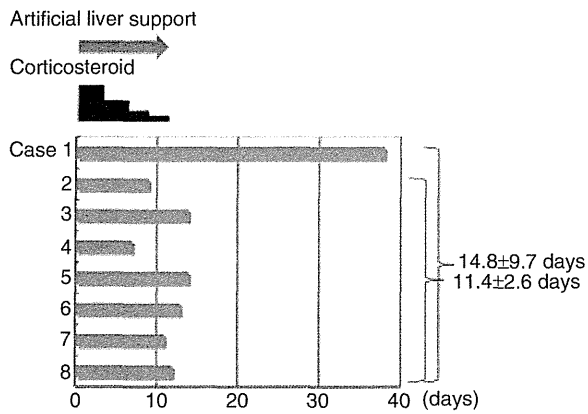

Figure 1 | The duration between the introduction of corticosteroids and the onset of sepsis in our patients with fulminant autoimmune hepatitis.

The survival rate without liver transplantation (LT) of patients with fulminant AIH is poor,[2, 5] which is recognised everywhere around the world. LT should be considered, but in Japan where the serious problems of a shortage of donor livers exist, the treatment decision against immunosuppressive therapy is difficult. Czaja suggested that failure to improve within 2 weeks of immunosuppression indicates the need of emergency LT.[6]

We applaud his efforts for diagnosing and treating this intractable liver disease, and dare to present one uncertain but important data based on 'low-quality clinical evidence and conflicting experiences', as hepatologists struggling against intractable liver diseases, including AIH, in Japan. Mean duration between introduction of immunosuppression and onset of sepsis was 14.8 ± 9.7 days in our autoimmune ALF patients (Figure 1). Therefore, we also suppose that the 2-week duration after introduction of immunosuppression is indeed a critical point for avoiding infectious complications and considering LT, although the most important treatment strategy is to diagnose and treat acute onset AIH before the development of ALF.[5]

ACKNOWLEDGEMENT

Declaration of personal and funding interests: None.

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Letter: treatment of autoimmune acute liver failure – beyond consensus guidelines; author's reply

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doi:10.1111/apt.12498

SIRS, Dr Fujiwara and colleagues emphasise three key concepts in the diagnosis and management of acute severe (fulminant) autoimmune hepatitis.[1] First, its occurrence is underestimated in most experiences. The abrupt onset of the disease may not allow the classical phenotype to emerge, and patients may lack hypergammaglobulinemia, high titres of autoantibodies and classical histological patterns.[2] Furthermore, the concept that an archetypal form of chronic hepatitis can present *de novo* as acute liver failure may not be uniformly entrenched in clinical practice.

Second, the diagnosis can be difficult. Classical features may be absent or altered; diagnostic scores by the comprehensive international scoring system may be low; and liver tissue examination may be avoided.[3] Doctor Fujiwara and colleagues have already emphasised the importance of liver tissue assessment in the evaluation of these patients,[4] and they have indicated that the presence of heterogeneous hypoattenuated areas within the liver by unenhanced computerised tomography is another means of supporting the diagnosis.[5]

Third, corticosteroid therapy can be life-saving, but it cannot be indefinite. Septic complications can occur and jeopardise the opportunity for successful liver transplantation.[6] Patients with multilobular necrosis at presentation who fail to improve at least one liver test within 2 weeks of treatment[7] and icteric patients who do not improve mathematical models of end-stage liver disease by at least 2 points within 7 days of therapy have dismal outcomes,[8] and they must be considered for liver transplantation. Worsening of any feature during treatment also compels this intervention. A decision regarding the appropriate strategy must be made within 7–14 days.[9]

The Japanese experience has taught us much about the nature and behaviour of autoimmune hepatitis, and we are indebted to Dr Fujiwara and colleagues for their insights.

ACKNOWLEDGEMENT

The author's declarations of personal and financial interests are unchanged from those in the original article.[10]

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Clin J Gastroenterol (2013) 6:465–469
DOI 10.1007/s12328-013-0423-9

CASE REPORT

A case of primary biliary cirrhosis and autoimmune hepatitis overlap showing acute presentation and transient seropositivity for immunoglobulin G and anti-nuclear antibody

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Received: 15 July 2013 / Accepted: 27 August 2013 / Published online: 8 September 2013

Abstract Autoimmune hepatitis (AIH) is generally regarded as a clinically and histologically "chronic" hepatitis. It often shows acute presentation like acute hepatitis without typical clinicopathological features of AIH, especially in a case of overlap with primary biliary cirrhosis (PBC). A 52-year-old man showed mild liver dysfunction for the first time at an annual medical check. Two months later, he showed jaundice, and laboratory tests revealed elevation of liver enzymes, hyperbilirubinemia and prolonged prothrombin time activity like acute liver failure. Anti-mitochondrial antibody was positive and other viral and autoimmune markers were negative. His liver function tests improved upon treatment with ursodeoxycholic acid and maximum intravenous glycyrrhizin (IVGL), but liver dysfunction was again exacerbated after the gradual reduction of IVGL. He showed transient elevation of immunoglobulin G (IgG) and anti-nuclear antibody (ANA) at only one point, and liver histology was compatible with PBC and AIH overlap syndrome. Corticosteroid was administered and his liver function tests returned to normal. It is important for the diagnosis of acute onset AIH to monitor IgG level and ANA titer, especially in patients without IgG and ANA elevations at first appearance.

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Keywords Primary biliary cirrhosis · Autoimmune hepatitis · Anti-nuclear antibody · Immunoglobulin G

Introduction

Autoimmune hepatitis (AIH) is generally regarded as a clinically and histologically "chronic" hepatitis, characterized by the presence of autoantibodies, hypergammaglobulinemia, and interface hepatitis and plasma cell infiltration on histological examination [1, 2]. It often shows acute presentation like acute hepatitis without typical clinicopathological features of AIH [3–8], especially in a case of overlap with primary biliary cirrhosis (PBC) [9, 10]. We report a case of PBC and AIH overlap that presented acute hepatitis and showed transient elevation of immunoglobulin G (IgG) and anti-nuclear antibody (ANA) at only one point.

Case report

A 52-year-old man showed liver dysfunction for the first time at an annual medical check, with aspartate aminotransaminase (AST) of 84 IU/l, alanine aminotransaminase (ALT) of 107 IU/l and gamma-glutamyl transpeptidase of 69 IU/l . Two months after that, he showed jaundice and laboratory tests revealed AST of 961 IU/l, ALT of 1280 IU/l, alkaline phosphatase of 306 IU/l, total bilirubin (T-BIL) of 8.6 mg/dl and prothrombin time (PT) activity of 62 %, and normal ultrasound findings, and was admitted to our hospital. IgM anti-hepatitis A virus antibody, hepatitis B virus (HBV) surface antigen, IgM anti-HBV core antibody, HBV DNA, second generation anti-hepatitis C virus (HCV) antibody, HCV RNA, hepatitis E virus RNA, IgM

anti-Epstein-Barr virus antibody, IgM anti-herpes simplex virus antibody, IgM anti-cytomegalovirus antibody, ANA, anti-smooth muscle antibody (ASMA) and liver kidney microsomal antibody-1 (LKM-1) were negative, and anti-mitochondrial M2 antibody (AMA M2) was positive (92.1, cut-off index). ANA and ASMA were examined by a fluorescent antibody method, and AMA M2 and LKM-1 were examined by an enzyme linked immunosorbent assay.

IgG was 1616 mg/dl and IgM was 210 mg/dl (Table 1). The patient had no history of recent exposure to drugs and chemical agents, and other etiologies including Wilson's disease were excluded. He also had no previous illness and no family history of autoimmune disease. International AIH score was non-diagnostic.

The patient's liver function tests improved treated with ursodeoxycholic acid and 100 ml/day of intravenous glycyrrhizin (IVGL) [11], but liver dysfunction was again exacerbated after the gradual reduction of IVGL, showing ALT of 473 IU/l, T-BIL of 19.7 mg/dl and PT activity of 51 %. At that time, IgG increased to 2762 mg/dl and ANA became positive (1: 160) (Table 2; Fig. 1). Human leukocyte antigen-DR (HLA-DR) was 8 and 9. A liver biopsy was performed and revealed interface hepatitis with lymphocytic infiltration, centrilobular necrosis/collapse, plasma cell infiltration, rosette formation, cholestasis, and nonsuppurative destructive cholangitis, which was compatible with PBC/acute onset AIH overlap (Fig. 2). International AIH score indicated probable diagnosis by the revised original system [12], and definite diagnosis by the simplified system [13]. Overlap syndrome was diagnosed by Paris criteria [14]. Therefore, corticosteroid was administered and the patient's liver function tests returned to normal. One month after the exacerbation, IgG became normal and ANA negative again (Fig. 1). Ultrasound appeared normal during the course.

Discussion

There is no formal definition of PBC and AIH overlap syndrome. PBC and AIH overlap usually refers to patients with AMA-positive PBC followed by sequential or simultaneous AIH, and not to patients with AIH who have coincidental AMA, although previous studies so far reported are of insufficient size to indicate clear characteristics of overlap syndrome. Patients with overlap have a more severe disease and worse outcomes compared to those with PBC alone, in terms of complications of portal hypertension, death, or need for liver transplant [9, 10].

Acute presentations of AIH have been reported; clinical features cover a spectrum from mild to severe, fulminant hepatitis (acute liver failure; ALF) [3–8]. Nevertheless, it is very difficult to diagnose acute onset AIH, because some patients exist without hypergammaglobulinemia, autoantibodies and interface hepatitis and plasma cell infiltration on histological examination, and because of the lack of a gold standard for the diagnosis. Therefore, at present, some cases are diagnosed as cryptogenic hepatitis. In our study, IgG was normal in 35 % and ANA less than 1: 80 in 24 % of patients in the early stage of the disease [15]. Therefore, patients with acute onset AIH are at risk of losing the timing of starting immunosuppressive therapy, some of them develop into ALF in subacute clinical course, and are

Table 1 Laboratory data on admission

Hematology		*Biochemistry*		*Viral marker*	
WBC	5300/mm^3	TP	7.2 g/dL	IgM-HA	(−)
Neut	53.0 %	ALB	3.8 g/dL	HBs-Ag	(−)
Lym	38.0 %	T-BIL	8.6 mg/dL	IgM-HBc	(−)
Mono	9.0 %	D-BIL	6.3 mg/dL	HBV-DNA	(−)
Eosino	0.0 %	AST	961 IU/L	HCV-Ab	(−)
Baso	0.0 %	ALT	1280 IU/L	HCV-RNA	(−)
RBC	466 × 10^4/mm^3	LDH	492 IU/L	HEV-RNA	(−)
Hb	14.6 g/dL	ALP	368 IU/L	IgM-HSV	(−)
Hct	41.5 %	γ-GTP	580 IU/L	IgM-CMV	(−)
Plt	14.0 × 10^4/mm^3	NH3	67 μg/dL	IgM-EBV	(−)
Coagulation		T-Cho	204 mg/dL	*Immunology*	
PT	62 %	TG	83 mg/dL	IgG	1616 mg/μl
PT-INR	1.38	BUN	15.1 mg/dL	IgM	210 mg/dL
		Cre	0.76 mg/dL	ANA	<×40
		Na	138 mEq/L	ASMA	(−)
		K	4.3 mEq/L	LKM-1	(−)
		CRP	1.3 mg/dL	AMA M2	92.1
		AFP	<10 ng/dl		

Table 2 Laboratory data on exacerbation

Hematology		*Biochemistry*		*Immunology*
WBC	6500/mm^3	TP	8.1 g/dL	IgG 2762 mg/dL
Neut	54.0 %	ALB	3.0 g/dL	lgM 252 mg/dL
Lym	30.0 %	T-BIL	19 7 mg/dL	
Mono	11.0 %	D-BIL	14.0 mg/dL	ANA ×160 (homo, AMA)
Eosino	4.0 %	AST	462 IU/L	
Baso	1.0 %	ALT	473 IU/L	
RBC	460 × 10^4/mm^3	LDH	316 IU/L	HLA-DR 8, 9
Hb	15.2 g/dL	ALP	415 IU/L	
Hct	44.7 %	γ-GTP	162 IU/L	
Plt	13.4 × 10^4/mm^3	NH3	55 μg/dL	
Coagulation		T-Cho	204 mg/dL	
PT	51 %	TG	179 mg/dL	
PT-INR	1.65	BUN	7.6 mg/dL	
		Cre	0.78 mg/dL	
		Na	138 mEq/L	
		K	4.4 mEq/L	
		CRP	1.4 mg/dL	

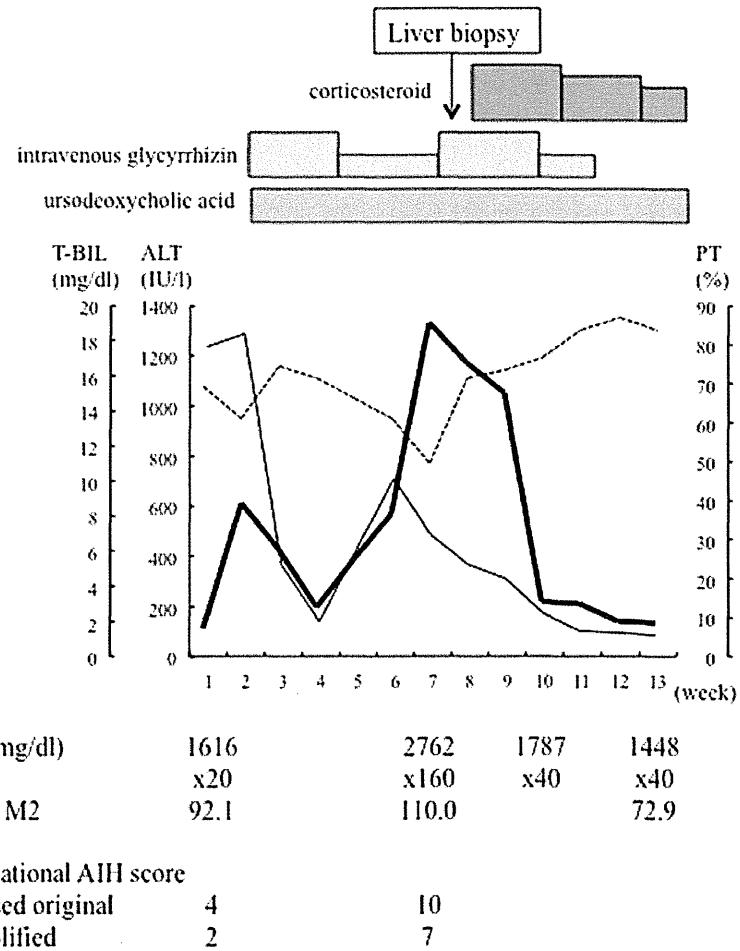

Fig. 1 Clinical course of the patient. *Thin solid*, *thick solid* and *dashed lines* denote ALT, T-BIL and PT, respectively. *UDCA* ursodeoxycholic acid, *IVGL* intravenous glycyrrhizin, *CS* corticosteroid, *ALT* alanine aminotransaminase, *T-BIL* total bilirubin, *PT* prothrombin time, *IgG* immunoglobulin G, *ANA* anti-nuclear antibody, *AMA* anti-mitochondrial antibody

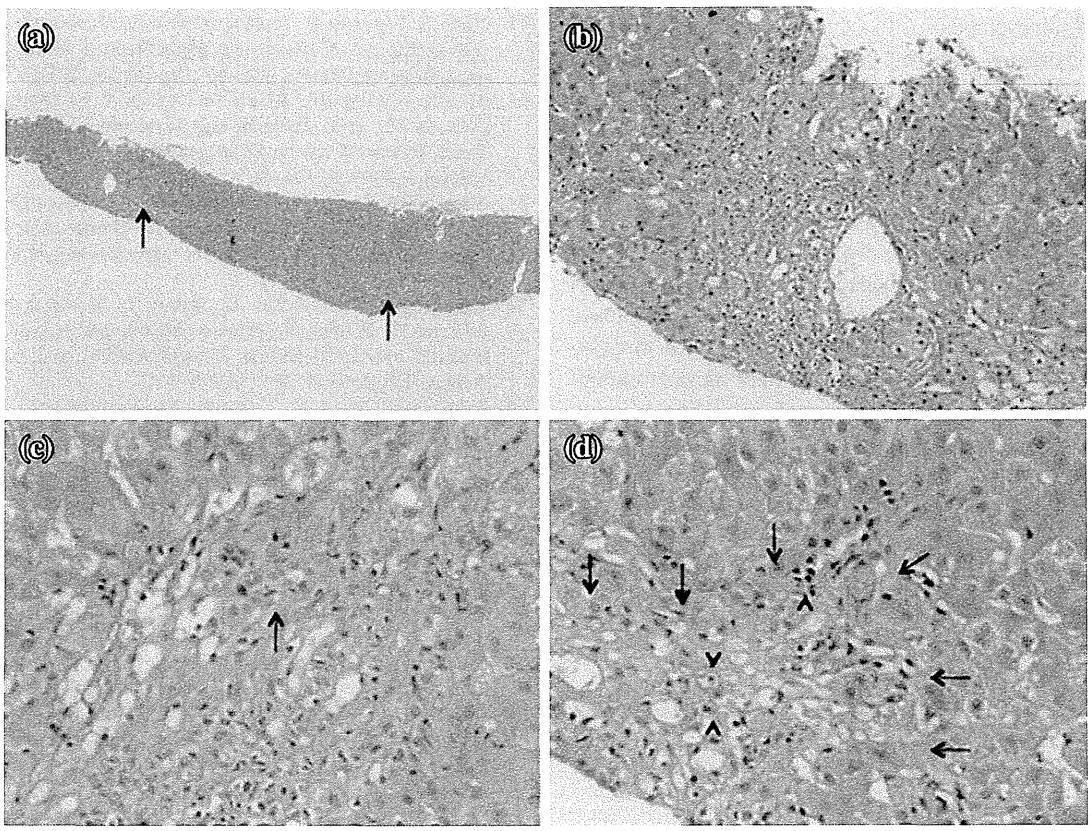

Fig. 2 Liver histology of the patient (HE stain). **a** Interface hepatitis with lymphocytic infiltration and centrilobular necrosis/collapse (*arrow*) are shown (×40). **b** Ductular reactions are seen in periportal area (×200). **c** Nonsuppurative destructive cholangitis (*arrow*) is seen (×400). **d** Centrilobular collapse (*arrow*) with plasma cell infiltration (*arrow head*) is seen (×400)

often resistant to immunosuppressive therapy and have poor prognosis. Survival rate of autoimmune fulminant hepatitis is 15 % without liver transplantation [7, 15, 16]. After establishment of the criteria by the International Autoimmune Hepatitis Group [12], the diagnosis of patients with AIH came to be made by a scoring system, and diagnosis of autoimmune ALF is also coming to be made by the system, as well as the recognition of acute onset AIH.

In a recent Japanese nationwide survey, the number of patients with AIH showing the histological features of acute hepatitis has been increasing [17], and AIH phenotype presenting with acute hepatitis and ALF was proposed by the Autoimmune Hepatitis Study Group of Japan [18]. The characteristic histological picture of acute onset AIH at the early stage of illness is centrilobular necrosis/collapse, an atypical histological pattern of AIH [6, 8, 15–26]. In our recent study of histological examination of acute onset AIH patients, 60 % showed acute hepatitis, exhibiting zonal, submassive and massive necrosis with or without plasma cell accumulation in portal and centrilobular areas, and 40 % showed chronic hepatitis, with the proportion of the acute form increasing significantly with disease severity [15].

Regarding the AIH scoring system by the international AIH group, the revised original scoring system [12] performed better in patients with acute onset AIH than the simplified scoring system [13], because acute onset AIH patients show low titers of auto-antibodies and low levels of IgG, and liver histology often showed acute hepatitis showing centrilobular necrosis/collapse, with lower points in the simplified scoring system as a result [27]. The simplified system was useful in our present case because of overlap syndrome.

Fortunately, we could diagnose our patient because he showed transient elevation of IgG and ANA at only one point. Histology was compatible with PBC and AIH overlap. The diagnosis and introduction of corticosteroid might have been difficult without scoring systems, and he would have developed into ALF without them. We think it important for the diagnosis of acute onset AIH to monitor IgG level and ANA titer periodically, especially in patients without IgG and ANA elevations.

A pathological characteristic of acute onset AIH is its 'heterogeneity', especially in ALF. Histological heterogeneity leads to radiological heterogeneity, although this finding was not found in our present case. Unenhanced

computed tomography (CT) often shows heterogeneous hypo-attenuations reflecting histological massive hepatic necrosis. This finding could be one of the tools for diagnosing acute onset AIH, especially autoimmune ALF [28].

In order to diagnose patients with acute onset AIH or PBC and AIH overlap, we should use the international AIH scoring system properly, after excluding other causes systematically, including viral hepatitis, drug-induced liver injury, non-alcoholic steatohepatitis and so on. Histological examination of the liver is necessary for early diagnosis. With timely introduction of immunosuppressive therapy, prognosis could be improved without liver transplantation. The most important treatment strategy is to diagnose and treat acute onset AIH before it develops into ALF [15, 29].

Disclosures

Conflict of Interest: No conflicts of interest exist.

Human/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed Consent: Informed consent was obtained from all patients for being included in the study.

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Letter to the Editor

European Journal of Gastroenterology & Hepatology 2013, 00:000–000

Corticosteroid for severe acute exacerbation of chronic hepatitis B

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Received 6 September 2013 **Accepted** 9 September 2013

We read with interest the article by He *et al.* [1], who carried out a meta-analysis evaluating the safety, efficacy, and side effects of corticosteroid (CS) therapy for severe acute exacerbation of chronic hepatitis B (SAECHB). We found misreadings of our data, but we understand the authors' efforts to analyze huge heterogeneous and complicated data.

Surprisingly, in the most recent Japanese nationwide survey carried out between 2009 and 2010, none of the patients with fulminant liver failure because of SAECHB recovered without liver transplantation. There is no beneficial treatment, except for emergency liver transplantation for acute liver failure (ALF) because of SAECHB. However, in Japan, where the problem of shortage of donor livers still remains, therapies other than transplantation must be further investigated for the patients. Therefore, we have investigated therapies of patients with SAECHB and reported that the introduction of a sufficient dose and period of CS and nucleoside analog in the early stages of ALF was effective in suppressing the destruction of hepatocytes, which led to liver regeneration and survival [2–5].

CSs had been used since the initial uncontrolled successes in the 1950s and 1960s, but had no place in the management of ALF in the USA and European countries after controlled trials in the 1970s had shown no improvement in survival. Thereafter, effective antihepatitis B viral, antibacterial, antifungal, and antiviral agents, and H_2 blockers/proton pump inhibitors became available.

At this time, we should re-evaluate the efficacy of CS in combination with nucleoside analog in SAECHB by multicenter studies using 'uniform criteria and treatment protocols', although we cannot include placebo-controlled patients, considering the poor prognosis.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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0954-691X DOI: 10.1097/MEG.0000000000000000

Hepatology Research

Hepatology Research 2013; 43: 452–458 doi: 10.1111/j.1872-034X.2012.01092.x

Original Article

Nutritional management contributes to improvement in minimal hepatic encephalopathy and quality of life in patients with liver cirrhosis: A preliminary, prospective, open-label study

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Aim: Problems in patients with minimal hepatic encephalopathy (MHE) include episodes such as falls and deficient driving skills, without any recognition of neurophysiological dysfunction. Patients with MHE are also more likely to develop overt hepatic encephalopathy. However, there is not yet any interventional strategy for MHE involving nutritional management. We conducted a preliminary study to investigate the proportion of positive MHE and the effects of nutritional management on MHE.

Methods: Patients with viral liver cirrhosis and abnormal neuropsychological tests were included. Nutritional consultations were conducted periodically by a dietitian, who recommended 30–35 kcal with 1.0–1.5 g of protein/kg of ideal bodyweight/day. The primary end-point was to evaluate the proportion of patients who recovered from MHE. The secondary end-point was to evaluate the improvement in the patients' quality of life (QOL).

Results: Thirty-two (30.1%) of 106 patients were diagnosed with MHE. Nineteen patients were enrolled in the study. Eleven of 19 patients became non-MHE after 4 weeks, and 13 of 19 patients (68.4%, $P < 0.001$) after 8 weeks. The mental summary scores were significantly improved at 8 weeks ($P = 0.0413$). Changes in albumin levels from week 0 to week 8 were 0.15 ± 0.16 g/dL in the improved MHE group and -0.28 ± 0.33 g/dL in the non-improved MHE group, which differ significantly ($P = 0.0130$).

Conclusion: Periodical nutritional management improved MHE and QOL. Improving the patient's nutritional condition may be one approach to treating MHE.

Key words: chronic liver disease, cirrhosis, hepatic encephalopathy, neuropsychological, nutrition

INTRODUCTION

MOST PATIENTS WHO are infected with hepatitis C virus progress to liver cirrhosis (LC). LC induces various clinical phenomena, such as

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Conflict of interest: Hisataka Moriwaki has served as a speaker for Otsuka Pharmaceutical and Ajinomoto Pharmaceutical, and received research funding from Otsuka Pharmaceutical, Ajinomoto Pharmaceutical, Astellas Pharmaceutical, Kyorin Pharmaceutical, MSD, Daiichi Sankyo and Chugai. Takumi Kawaguchi has affiliations with a donation-funded department of MSD.

Received 25 June 2012; revision 16 August 2012; accepted 21 August 2012.

malnutrition, overt hepatic encephalopathy (HE) and hepatic coma. Recently, minimal hepatic encephalopathy (MHE) was reported, and can be defined as a subclinical form of HE. MHE can be present in LC patients who are clinically normal but who show abnormalities in cognition and/or neurophysiological variables. Problems in patients with MHE include episodes such as falls and deficient driving skills, with no recognition of neurophysiological dysfunction. In a retrospective observational study, Román *et al.* reported that the incidence of falls was 40% in LC patients with MHE, but only 12.9% in those without MHE.[1] Bajaj *et al.* reported that the assessment of the driving skills of patients with MHE differed significantly between the patients themselves and the observers ($P = 0.02$). This finding indicates that patients with MHE have poor insight into their driving deficiencies.[2] MHE is considered relevant to health-related quality of life (HRQOL).[3–5] Therefore, a higher incidence of falls and driving accidents would imply an increase in economic and social costs. Patients with MHE are also more likely to develop overt HE. Romero-Gómez *et al.* demonstrated that 19 (30%) of 63 patients with MHE developed overt HE during follow up. In a Cox regression analysis, MHE was an independent variable predicting HE.[6] Therefore, it may be necessary to diagnose MHE to avoid these risks.

Neuropsychiatric and neurophysiological tests are reported as the diagnostic modality of MHE. Neurophysiological tests have relative advantages in terms of the lack of learning effects and the relative specificity of the response. However, a psychologist is required for administration and interpretation. In addition, electroencephalography is an expensive modality. Neuropsychiatric testing, recommended by a consensus statement of the International Society for the Study of Hepatic Encephalopathy and Nitrogen Metabolism, is a modality to confirm cognitive impairment. These tests become difficult to apply in a regular setting. Therefore, we developed a simple computer-aided neuropsychiatric test (NP-test) system, consisting of eight tests that can be performed easily by outpatients using a touch panel. We also established national standard criteria for the diagnosis of MHE in LC patients.[7] However, it takes almost 30 min for outpatients to complete the eight tests of the NP-test. The Working Party at the 11th World Congresses of Gastroenterology, Vienna, in 1998 stated the need for a shorter evaluation, leading to the use of four tests: (i) the number connection test A (NCT-A); (ii) number connection test B (NCT-B); (iii) digit symbol test (DST); and (iv) block design test (BDT).[8] The BDT and DST are subtests of the Wechsler Adult Intelligence Scale – Revised (WAIS–R). In the present study, these four tests were selected from the NP-test for patient assessment.

More recently, several candidate therapeutic interventional strategies for MHE have been reported, including supplementation of lactulose, rifaximin and acetyl-L-carnitine.[9,10] Mullen *et al.* explained by describing an algorism for treating HE. The primary therapeutic strategy in patients with HE is administration of lactulose. If this therapy has insufficient effect, nonabsorbable antibiotics are recommended. Moreover, for patients with inadequate response to these therapies, decreasing animal protein intake and using branched-chain amino acid (BCAA)-enriched formulations are suggested as optimal therapeutic strategy.[11] In this regard, nutritional management is required in these patients with HE. However, the effect of nutritional management on neuropsychological testing has not been observed yet.

We conducted a preliminary study to investigate the proportion of positive MHE and the effect of nutritional management on neuropsychological testing for positive MHE patients with LC in Japan.

METHODS

Subjects

THIS STUDY WAS approved by the ethics committees of 17 affiliated organizations in Japan. Written informed consent was obtained from all the participants. Viral LC patients (diagnosed by computed tomography or ultrasonography) who were younger than 70 years old, not obviously HE, were enrolled in the study. The exclusion criteria were a history of HE, treatment for transjugular intrahepatic portosystemic shunt[12] or esophagogastric varices.

Study design

The cirrhotic patients were examined with the NP-test to confirm MHE. Positive MHE was defined as abnormal test results for more than two of the subtests of the NP-test, including the BDT, DST, NCT-A and NCT-B. We referred to the report by Michitaka *et al.*, which stated that two or more abnormal tests on the NP-test were required for a diagnosis of MHE with 80% specificity.[13] Cirrhotic patients with positive MHE underwent a periodic nutritional consultation with a dietitian. The nutritional consultation recommended 30–35 kcal with 1.0–1.5 g of protein/kg of ideal bodyweight/day,

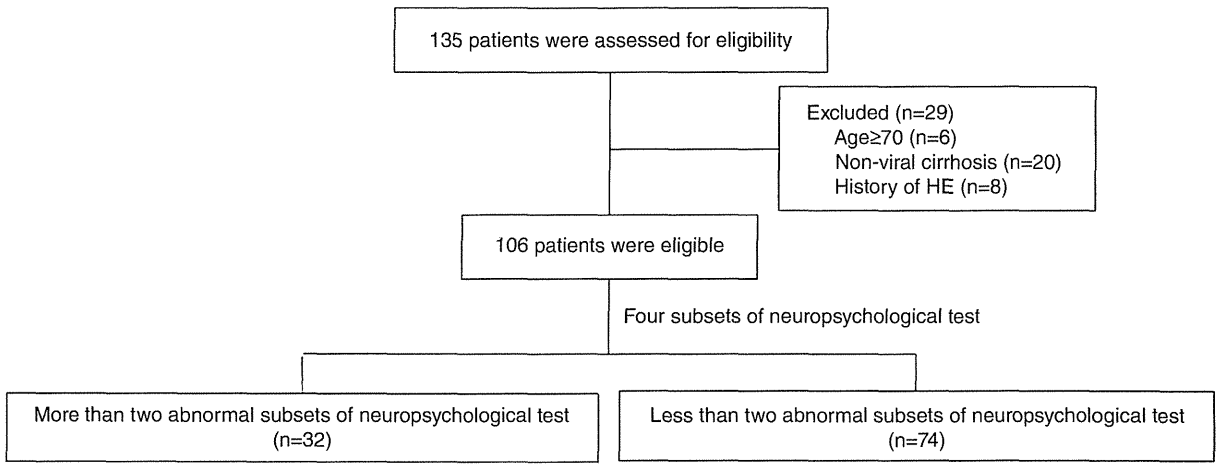

Figure 1 Patient flow. HE, hepatic encephalopathy.

according to the European Society of Parenteral and Enteral Nutrition (ESPEN) guideline,[14] the avoidance of a fasting diet and a recommendation for frequent meals. Dietitian consultation was performed at least once during the study period. The other treatments for LC such as BCAA, lactulose, non-absorbable antibiotic and probiotic treatments were not restricted. The NP-test, 8-item Short Form Health Survey (SF-8) and laboratory tests were performed at 0, 4 and 8 weeks. Laboratory tests were performed in the morning after overnight fast. MHE was defined as more than two abnormal subsets of NP-test.

End-points

The primary end-point was to investigate the proportion of positive MHE and the effect of nutritional management on neuropsychological testing for positive MHE patients with LC in Japan. The secondary end-point was to evaluate the improvement of SF-8 scores and clinical parameters as a result of nutritional management for 8 weeks.

Statistical analysis

The proportion of patients who became non-MHE after 4 and 8 weeks was compared with that at week 0 using McNemar's test. The values are given as absolute differences (AD) and 95% confidence intervals (95% CI). Changes in the SF-8 scores and nutritional parameters were analyzed by Wilcoxon rank sum test or the Mann–Whitney *U*-test. Statistical significance was defined as $P < 0.05$. The statistical analysis was performed with JMP software ver. 8.0.2 (SAS Institute, Cary, NC, USA).

RESULTS

WE OBTAINED INFORMED consent from 135 patients with LC. Twenty-nine patients were excluded: four were more than 70 years old, 15 had non-viral cirrhosis, five had history of HE, two were more than 70 years old and had non-viral cirrhosis, and three had non-viral cirrhosis combined with history of HE. One hundred and six patients were eligible and were assessed by four subsets of the NP-test (Fig. 1). Thirty-two (30.1%) of 106 patients with viral LC were diagnosed positive for MHE. The characteristics of positive and negative MHE patients with viral LC are shown in Table 1. Thirteen patients withdrew during the study period: one patient deviated from the study protocol, two had hepatocellular carcinoma, one had lung cancer, one had colon cancer, one was prescribed interferon, one patient progressed to obvious HE, one patient died of hepatocellular carcinoma, one died of aggravated of ascites, and four stopped attending the hospital. Therefore, 19 patients completed the study protocol and were analyzed.

Effects of nutritional consultation

Eleven of the 19 patients had become non-MHE (AD = 57.8%, 95% CI = 35.6–80.0, $P < 0.001$) at 4 weeks and 13 of 19 (AD = 68.4%, 95% CI = 47.5–89.3, $P < 0.001$) at 8 weeks by nutritional consultation (Table 2).

The mental summary scores assessed with SF-8 were significantly improved at 4 and 8 weeks ($P = 0.0295$ and $P = 0.0413$, respectively). The scores for physical functioning, physical role, bodily pain, general health,

Table 1 Patient characteristics of positive and negative MHE

	Positive MHE ($n = 32$)	Negative MHE ($n = 74$)	
	Median (range)	Median (range)	
Sex (male/female)	15/17	45/29	N.S.
Age (years)	62.0 (42.0–69.0)	62.0 (44.0–69.0)	N.S.
Height (cm)	160.3 (140.0–179.0)	161.7 (39.0–180.0)	N.S.
Weight (kg)	58.2 (42.0–86.6)	64.0 (41.4–93.0)	N.S.
Hepatocarcinoma (yes/no)	5/27	17/57	N.S.
Varix (yes/no)	3/29	13/61	N.S.
Ascites (yes/no)	1/31	2/72	N.S.
Child–Pugh (A/B/C)	16/13/3	43/17/7	N.S.
Disaccharide (yes/no)	6/25	10/63	N.S.
Branched-chain amino acid granules (yes/no)	12/20	21/53	N.S.
Albumin (g/dL)	3.4 (2.0–4.7)	3.3 (1.7–4.5)	N.S.
Branched-chain amino acids per tyrosine	3.2 (1.3–7.3)	3.2 (1.67–7.6)	N.S.
Cholinesterase (IU/L)	116 (42–273)	149 (41–460)	N.S.
Total bilirubin (mg/dL)	1.1 (0.3–5.0)	1.1 (0.3–4.7)	N.S.
Fasting blood sugar (mg/dL)	107 (79–232)	105 (58–283)	N.S.
Ammonia (mg/dL)	65 (14–269)	53 (16–146)	N.S.
Blood urea nitrogen (mg/dL)	13.0 (5.0–25.0)	13.7 (5.0–71.0)	N.S.
Creatinine (mg/dL)	0.63 (0.40–1.04)	0.71 (0.45–2.94)	N.S.

MHE, minimal hepatic encephalopathy; N.S., not significant.

vitality, social functioning, emotional role and mental health are shown in Figure 2.

The clinical parameters of the patients with improved MHE and those without improved MHE were compared (Table 3). The changes in albumin levels from week 0 to week 8 were 0.15 ± 0.16 g/dL in the improved MHE group and -0.28 ± 0.33 g/dL in the non-improved MHE group, which differ significantly (AD = 0.43, 95% CI = 0.21–0.66, $P = 0.0130$). The baseline levels of BCAA and tyrosine ratio (BTR) were 4.59 ± 1.31 in the improved MHE group and 2.13 ± 0.58 in the non-improved MHE group, which differ significantly (AD = 2.46, 95% CI = 1.05–3.87, $P = 0.0058$). The changes of clinical parameters (BTR, prothrombin, total bilirubin, ammonia, blood urea nitrogen and creatinine) were not statistically significant compared with the patients with improved and non-improved MHE.

Table 2 Change in number of patients diagnosed positive and negative MHE by neuropsychiatric tests

	No. of abnormal tests	No. of patients ($n = 19$)		
		Pre	4 weeks	8 weeks
Non-MHE	0	0	5 (26.3)	8 (42.1)
	1	0	6 (31.6)	5 (26.3)
MHE	2	12 (63.2)	5 (26.3)	4 (21.1)
	3	5 (26.3)	2 (10.5)	2 (10.5)
	4	2 (10.5)	1 (5.3)	0
Changing to non-MHE			11 (57.9)	13 (68.4)
Absolute difference			57.9	68.4
95% CI			35.6–80.0	47.5–89.3
P-value			<0.001	<0.001

Non-MHE was defined as the patients diagnosed as having <2 abnormal neurophysiological tests. Positive MHE was defined as the patients diagnosed as having ≥2 abnormal neurophysiological tests.
CI, confidential interval; MHE, minimal hepatic encephalopathy.

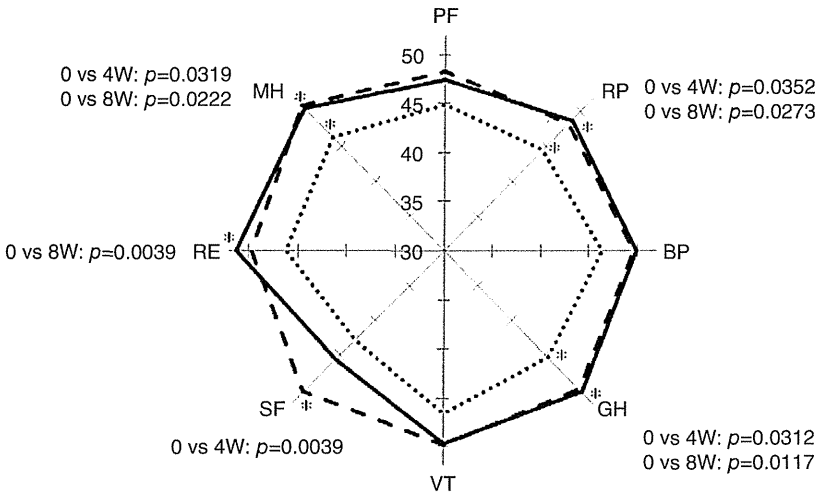

Figure 2 Effect of nutritional management on quality of life ($n = 19$). BP, bodily pain; GH, general health; ME, mental health; PF, physical functioning; RE, emotional role; RP, physical role; SF, social function; VT, vitality. ·····, Pre; – – –, 4 weeks; ——, 8 weeks.

DISCUSSION

THIS IS THE first study to investigate the effect of nutritional management on neuropsychological testing and quality of life (QOL), instituted by periodic consultations with patients with MHE. In this study, 32 of 106 patients (30.1%) were diagnosed with MHE. In previous studies, the prevalence of MHE has been reported in the range of 20–50%.[7,15,16] This wide range is attributable to the different criteria and devices used to diagnose MHE in these studies, including spectral electroencephalography. Rose *et al.* also reported that MHE represents several syndromes, some of which are reversible and some of which are not.[17] Therefore, adequate criteria for the accurate diagnosis of MHE are required.

In the present study, periodic nutritional consultations with a dietitian (who advised an intake according to the ESPEN guideline,[14] avoidance of a fasting diet and frequent meals) improved the MHE of 13 of 19 patients (68.4%). Vaisman *et al.* reported that the cognitive function and executive function of patients with MHE was improved by breakfast and by avoiding missing meals.[18] Miwa *et al.* reported that taking food with the necessary proteins and energy improved not only the energy metabolism of the patients but also the nutritional parameters assessed.[19] In our study, patients whose MHE improved showed improvements in their albumin levels. All the patients whose serum albumin levels improved showed improved MHE (data not shown). However, not all the patients with improved MHE showed improved serum albumin levels. It is unclear why this discrepancy occurred. The relationship between MHE and the nutritional condition of the patient is also unclear. Rose *et al.* suggested that both reversible and irreversible MHE may exist.[17] Long-term follow up of the non-improved MHE patients may be insightful. Furthermore, baseline BTR levels in patients with improved MHE were significantly higher compared with non-improved MHE. To improve MHE, not only increased albumin levels but also higher levels of BTR at baseline may be necessary (Table 3).

Table 3 Clinical parameters in relation to improvement of MHE ($n = 19$)

	Improved MHE ($n = 13$) (mean ± SD)	Non-improved MHE ($n = 6$) (mean ± SD)	AD	95% CI	*P*-value
Δ Albumin (g/dL)	0.15 ± 0.16	−0.28 ± 0.33	0.43	0.21–0.66	0.0130
Baseline of BTR	4.59 ± 1.31	2.13 ± 0.58	2.46	1.05–3.87	0.0058

Δ Albumin, post-albumin level – baseline of albumin level.
AD, absolute difference; BTR, branched-chain amino acid per tyrosine; CI, confidential interval; SD, standard deviation.

The mental summary score of the SF-8 was statistically significantly improved by the nutritional management. Recently, Sidhu *et al.* reported that improvement on the NP-test correlated with improvement in HRQOL.[5] Some variables are known to correlate with HRQOL in LC, such as ascites, muscle crump and abstinence.[20,21] Okumura *et al.* reported that HRQOL was improved by long-term late-evening snacks and by taking frequent meals.[22] Nakaya *et al.* reported that not only the nutritional parameters but also the subjective symptoms of patients with LC improved when they received late-evening supplementation with a BCAA-enriched nutrient mixture.[23] The MHE of five of 13 patients improved when they took the BCAA-enriched nutrient mixture as a late-evening snack. Nutritional status, serum albumin level, was significantly improved in the improved MHE group by nutritional management for 8 weeks. This result may show that improvement of MHE is not only correlated with QOL but also improvement of nutritional status. Therefore, improvements in MHE and HRQOL may be attributable to improvements in the patients' nutritional status.

The limitations of this study include the lack of a comparative design, the small sample size and the short study period. Moreover, the correlation between change of the number of abnormal tests by NP-test and clinical outcomes (prognosis, QOL, fall, driving skill and incidence of obvious HE) have not been evaluated yet. Moreover, Bajaj reported that HE mental status can fluctuate over time.[24] Rose *et al.* also reported that some cases of MHE are reversible and some are not.[17] Furthermore, the patients' characteristics such as Na, K, Cl and C-reactive protein levels were not measured. It is well known that a relationship between imbalance of electrolyte levels and incidence of HE is common.[25] In future, it will be necessary to confirm the relationship between the number of abnormal subsets of NP-testing and clinical outcome by long-term observational study. Moreover, correlation with NP-testing and neurophysiological testing will be also investigated. In addition, measurement of serum electrolytes is necessary.

In conclusion, nutritional management may contribute to the improvement of MHE by improved nutritional status resulting in improved QOL. As future study, a randomized controlled study is needed.

ACKNOWLEDGMENTS

THIS STUDY WAS affiliated with Satoyoshi Yamashita, Social Insurance Shimonoseki Kosei Hospital; Naoto Maeda, Tottori University; Makoto Shiraki, Gifu University; Makoto Segawa, Yamaguchi University; Koichi Shiraishi, Tokai University Hospital; Yoshio Tokumoto, Ehime University; Kenichi Ikejima, Juntendo University; Akinobu Takagi, Okayama University; Naruhiko Nagata, Tokai University Ohiso Hospital; Kazutomo Suzuki, Dokkyo Medical University Koshigaya Hospital; Yasuharu Imai, Tokyo Medical University; Daiki Habu, Norifumi Kawada, Osaka City University; and Satoshi Mochida, Saitama Medical University.

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