IAIHG recommends the indirect immunofluorescence method with frozen sections of rodent liver, kidney, and stomach to check for autoantibodies involved in AIH[18], this method is now used only at a limited number of institutions ; a larger number of institutions have adopted enzyme-linked immunosorbent assay (ELISA) or a method using established cell lines. The method recommended by the IAIHG can also reliably detect type 2 AIH and should, ideally, be adopted by all institutions. However, we believe this method is unlikely to easily gain widespread acceptance.

We have shown that the sensitivity for ANA in patients with AIH is lower with the ANA-ELISA kit widely used in Japan than with the indirect fluorescent antibody method with frozen rodent sections (data not shown). This lower specificity can probably be attributed to the antigen set contained in the common ANA-ELISA kit being designed for the diagnosis of systemic lupus erythematosus rather than of AIH. Using ELISA for screening for AIH is, therefore, inappropriate. Although a kit for the indirect fluorescent antibody method using the HEp-2 cell line has also been widely used, it has several problems, such as a lack of consistency in the HEp-2 cell cycle among different measurement sessions and a high false-positive rate due to excessively high sensitivity. An ELISA kit incorporating a solid layer, composed of HEp-2 cell nucleus components, and an additional ELISA antibody is also available, but its validity has not been sufficiently verified by assessing the consistency of results with the original rodent frozen sections. For the time being, it seems rational to use ELISA and cultured HEp-2 cells to assay ANAs only as a means of confirming the results from the original method and for following the clinical course of patients.

In practice, the American Association for the Study of Liver Diseases Guidelines on AIH, published in 2010[18], also adopted an indirect fluorescent antibody technique with rodent frozen tissue as the basic procedure for detecting ANAs. In any event, the method for autoantibody detection should be standardized and quantified.

Diagnosis of the Acute Onset, Overlap, IgG-4-Related Form of AIH

AIH is a chronic disease, but cases of acute onset are sometimes seen[19]. Clinical manifestations, including his-

tological findings, specific for AIH are lacking in cases of acute onset.

The pathophysiologic features of IgG-4-related AIH[20] and of the overlap of AIH with primary sclerosing cholangitis have been reported as new disease entities associated with AIH[21]. Particularly difficult are diagnosing AIH in children and distinguishing AIH from primary sclerosing cholangitis[22]. AIH accompanied by bile duct disease and the overlap of AIH with primary biliary cirrhosis have also been described as cases of AIH with clinical problems related to treatment[23]. Such cases are difficult to diagnosis with current diagnostic criteria, which focus on cases with typical manifestations. An important unresolved issue is how to make a rapid and precise diagnosis in these atypical cases. To solve this problem, we created a 7-variable formula based on 3 laboratory tests and 4 histological features to distinguish AIH from primary biliary cirrhosis and overlap syndrome[24].

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自己免疫性肝炎の診断・治療における最近の知見

銭 谷 幹 男*

要　旨

　最近の我が国の全国集計により，自己免疫性肝炎の診断数は増加していることが明らかとなっている．一方，従来臨床的特徴とされた IgG 上昇，血清自己抗体の高力価陽性所見に乏しい非定型とも言える症例の増加や，慢性肝炎像を伴わない急性発症型の存在は，薬物性肝障害との鑑別診断を含め，診断指針の再検討の必要性を示している．我が国で臨床的に使用されているウルソデオキシコール酸の意義についても明確な指針が求められている．

は　じ　め　に

　自己免疫性肝炎（AIH）の成因は，多くの研究にもかかわらず現在なお不明であり，結果として AIH と診断可能な特異的臨床指標は確立されていない．現状では既知の肝障害の要因を除外し，特異性はないが，AIH に高頻度で認められる血清 IgG 上昇，抗核抗体（ANA）をはじめとする血清自己抗体陽性所見，組織学的に形質細胞浸潤を伴う活動性の高い門脈域を中心とする炎症所見などから診断がなされている．国際診断スコア[1]はこれら診断に有用な諸所見を数量化して，AIH と診断可能な病態領域を囲い込むものである．我が国の診断指針にも記載されているように，このポイントは診断上参考にはなるが，ポイ

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　　　　　　副腎皮質ステロイド，
　　　　　　オーバーラップ症候群，
　　　　　　ウルソデオキシコール酸

ントが条件を満たしたことが AIH の診断を100％担保するものでもない．簡易型診断スコア[2]は，国際診断スコアが臨床上ベッドサイドで応用するには煩雑で，このスコアの項目を満たすために診断が遅れることを勘案して策定されたものである．したがって，簡易型診断スコアは早期の治療介入を容易にすることに重点が置かれ，抗ミトコンドリア抗体（AMA）による鑑別が排除されていることから，結果として原発性胆汁性肝硬変（PBC）で肝細胞障害が高度の症例も，AIH 同様に副腎皮質ステロイド（CS）治療適応と診断されることとなる．いずれのスコアにおいても，組織学的所見，血清自己抗体，特に ANA 所見はスコアのポイント上重要な要素となっている．2009 年に我が国で行われた全国集計により[3]，上記に示した重要な臨床所見の特異性が低下している事実が明らかにされた．この事実は，AIH の診断がより困難になっていることを示すものである．一方，C 型肝炎ウイルス（HCV）の診断が確立したことに

図1　我が国の自己免疫性肝炎症例の年齢分布

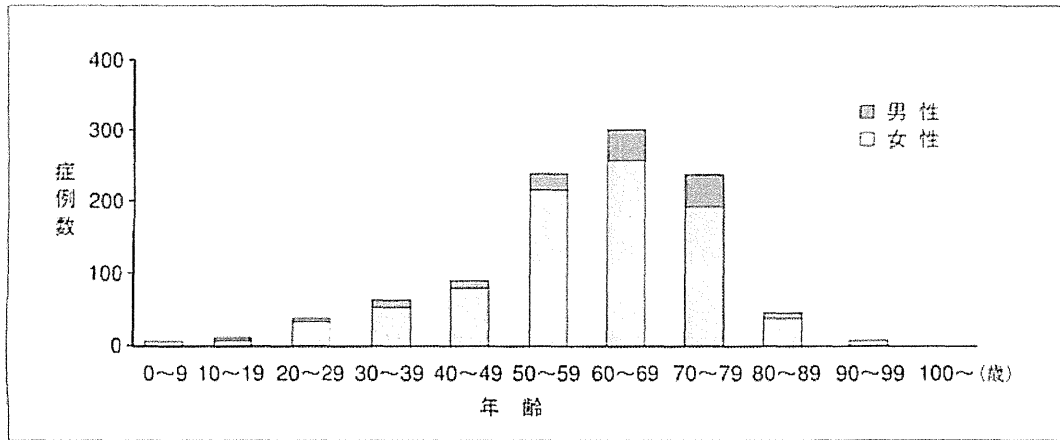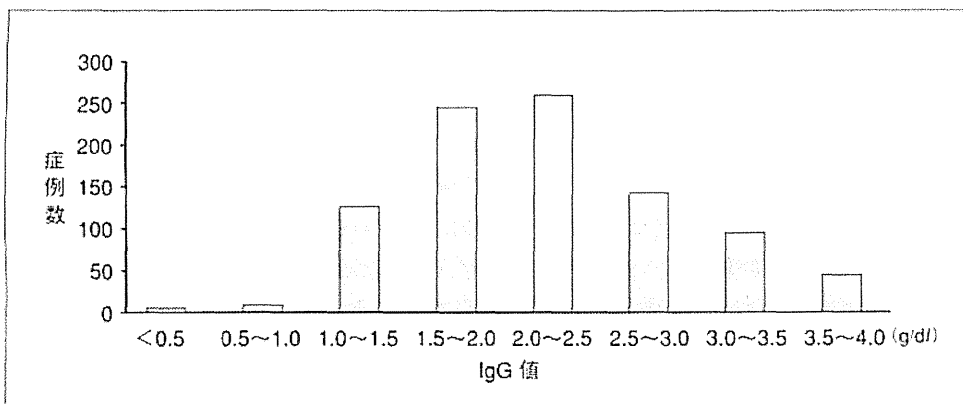

図2　診断時血清 IgG 値の分布

より，肝炎ウイルス感染によらない AIH を含む原因不明の肝細胞障害症例の診断数は増加しているという現状がある.

　本稿では，最新の我が国における全国集計の結果を示し，治療を含めた現状での問題点を含めて概説する.

<div style="text-align:center">最新の全国集計による我が国の
自己免疫性肝炎（AIH）の臨床像</div>

　図1〜3に全国集計結果の概要を示した．図1で明らかなように，診断時年齢は 60 歳をピークとする一峰性を呈し，50 歳，70 歳代が次いで高率である．すなわち，我が国の AIH 症例は人口高齢化と同様に高齢化して

いると言える．この事実は，高齢女性に原因不明の肝障害を認めた場合は AIH を念頭に置く必要性を示しているとも言える．なお，男女比は 1：6 で女性優位であることは従来と同様である．図2，3で明らかなように診断時の IgG 値，ANA 力価は以前の報告に比較して低値である．我が国の診断指針で示されている血清 IgG 値が 2.0g/dl 以上を満たさない症例が多く，かつ ANA が陰性の症例も少なからず認められる．血清 IgG に関しては，簡易型スコアで提唱されている基準値上限の 1.1 倍以上を当てはめてもこれを満たさない症例が少なからず存在し，かつ臨床的に診断され，治療されているという事実

図3　診断時血清抗核抗体力価の分布
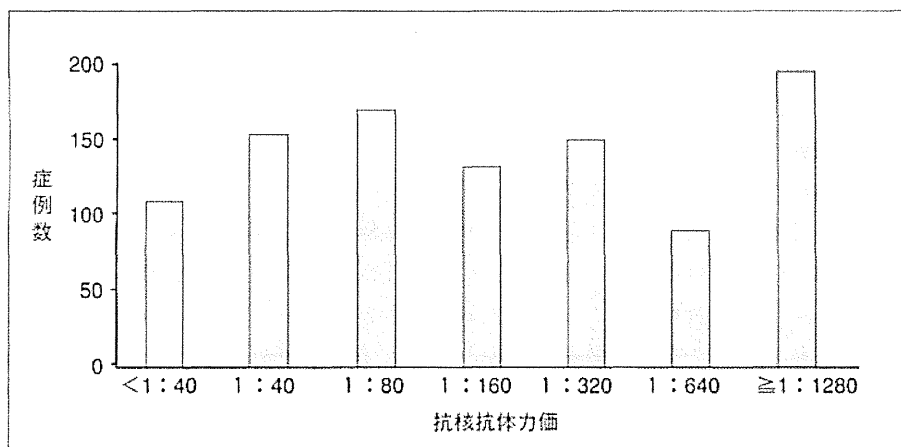
である．IgG 値の変化の要因には測定系の変化も勘案されるが，従来には非定型とされている症例の増加に対しては新たな診断指針の提唱が不可欠である．

抗核抗体（ANA）測定について

AIH の診断に際し，ANA はげっ歯目の新鮮凍結組織を用いた間接蛍光抗体法（IF 法）で測定することが国際自己免疫性肝炎グループより提唱され，最近の米国肝臓学会のガイドラインでも同様の趣旨が記載されている．しかし，我が国でこの方法を用いて ANA を測定している施設はほとんどなく，多くは樹立化細胞株である Hep-2 細胞を用いた IF 法で測定されている．両者の間には感度に差異があり，また凍結組織，培養細胞の生存状態など，標準化には多くの問題がある．しかし筆者らの検討では，Hep-2 細胞を用いた検討により，少なくとも ANA 検出に関しては診断上大きな齟齬が認められないことが明らかとなっている．一方 ANA 測定に関しては，定量性，特異性が優れていることから酵素結合免疫吸着法（ELISA）も汎用されている．しかし，我が国で汎用されている ELISA 法は，Hep-2 細胞による測定に比較し，AIH での検出感度は明らかに劣る

という問題がある．我が国で使用されている ANA-ELISA の抗原は，他の自己免疫疾患，特に全身性エリテマトーデス（SLE）などを対象に開発されたものであり，含有抗原には AIH における対応抗原が含まれていない可能性があるからである．事実，米国で汎用されている Hep-2 細胞核の抽出物を加えた ELISA 法は，我が国での ELISA に比較して AIH での ANA 検出感度は良好である．しかし凍結切片を用いた IF 法に比較すると，米国での ELISA も検出感度は十分とは言えない．したがって現状では，AIH の診断には既存の ELISA は不適であり，IF 法を用いることが必要であり，診断に当たって留意が必要である．

組織像について

AIH の肝組織の特徴は壊死・炎症反応で，インターフェイス肝炎を主体とし，浸潤細胞に形質細胞を含むことが特徴とされている．壊死・炎症が高度であることから，肝細胞ロゼット形成も高頻度で認められる．また，門脈域の炎症が高度の場合胆管障害も認められるが，胆管消失所見はまれである．しかし，いずれの所見も AIH に特異的とは言えないという問題がある．胆管障害が高度の場合，

PBC で肝細胞障害が高度の症例との鑑別は必ずしも容易でない．しかも，これら所見を記載する病理医の所見一致率，いわゆる κ 値が低いことも示されている．国際診断スコア，簡易型スコアともに組織所見はスコア確定上重要であるが，組織所見を参考に，臨床所見と併せて診断を進めることが重要である．なお，簡易型スコアでは AIH の組織所見の特徴として emperipolesis が提唱された．この所見は我が国ではあまりなじみがなく，組織所見として記載される頻度もまれであった．emperipolesis 所見を除外して従来の AIH の組織所見に符合することをもっても，簡易型スコアは十分有効なのであるが，emperipolesis は肝細胞内に単核球が侵入するという，免疫学的肝細胞障害を示す所見でもあり，今後標本の見直しを含め十分な再評価が必要である．

急性型 AIH

組織学的所見では AIH の急性発症型という新たな問題も提起されている．従来 AIH は慢性肝炎に分類され，急性発症のほとんどは慢性状態の急性増悪と理解されていた．したがって，肝組織は急性発症であっても，慢性肝炎像を示す．しかし，慢性肝炎像を全く伴わず，急性肝炎として発症する AIH 群が存在することが明らかとなり，全国集計でも組織学的に急性肝炎と診断された症例は 10% を超えている．臨床的には，AIH の特徴とされる IgG 高値，自己抗体陽性所見を欠き，診断は困難である．さらに組織学的所見でも，従来報告されている AIH の所見は認められず，報告例からは形質細胞浸潤を伴う，小葉中心の壊死・炎症反応を示すとされている．現状での診断指針，診断スコアでは，これらの診断は困難である．急性型 AIH に対しても，CS が通常の AIH 同様に著効を示す．しかし，診断が遅れ，病態が進展し，肝の壊死が高度になれば肝不全となり，治療奏効は期待できない．したがって，急性型 AIH は迅速な診断が必要であり，この解決が大きな課題である．

オーバーラップ症候群

PBC の経過中に肝細胞障害が増悪し，ANA 陽性化や IgG 上昇が認められた場合，従来はいわゆるオーバーラップ症候群として取り扱われることが多かった．こうした病態をオーバーラップ症候群として別の病態に層別化する意義は，治療対応が異なるからである．しかし，診断上は PBC の肝炎型として取り扱うことが妥当であることが提唱され，コンセンサスを得てきており，米国肝臓学会（AASLD）のガイドラインや我が国の検討でも同様の提唱がなされている．AMA 陰性で，組織学的に PBC に矛盾しないが，肝障害に対し CS が有効であることから，autoimmune cholangitis との病名を付与された病態も，実際は AMA 陰性 PBC の肝炎増悪型ととらえて何ら矛盾はなく，autoimmune cholangitis の病名は当初の提唱された概念としては取り扱わないのが妥当である．我が国での全国集計から導かれた判別式においてもこの事実は確認されている．一方 AIH と診断され，後に PBC 病態が顕性化する病態も報告されている．この病態は PBC で初期に肝細胞障害が顕性化したとも考えられ，実際は主たる病態は PBC とするのが多くの場合妥当である．

治療対応

CS の有効性は AIH の特徴でもあり，診断が確定されればその投与により，上昇していた血清 AST，ALT は速やかに改善し，多くの場合基準値以下になる．初期投与量に関してはプレドニゾロンで 0.5～1 mg/kg が妥当である．欧米の成書では 60mg/日の記

載が多いが，体格が異なる我が国ではそれよ
り少量で十分な効果が得られている．全国集
計では，初期量 30～40mg/日で 90% 以上の
症例で良好な効果が得られている．しかし少
数ながら CS 抵抗性症例も存在し，その場合
我が国では，保険収載はなされていないがア
ザチオプリン併用が多用されている．アザチ
オプリン使用に当たっては，代謝異常の遺伝
子背景を有する場合があることで急激な白血
球減少を見ることがあり，遺伝子検査，ある
いは血中濃度測定が必要である．我が国では
CS に加え，ウルソデオキシコール酸（UDCA）
が少なからず処方されている．UDCA 併用
は CS の減量に有効であることは確認されて
いるが，併用，非併用で長期予後，あるいは
再燃への影響はいまだ明確ではなく，今後の
検討が必要である．さらに，我が国では臨床
的活動性が低い，すなわち AST，ALT が低
値の症例に対しては UDCA のみの治療も行
われている．我が国では健診などにより，無
症状症例が AST，ALT 上昇によって捕捉
され，欧米では診断困難な AIH 初期あるい
は従来指摘がない病態が軽微で推移する症例
を扱っているとも考えられる．UDCA のみの
治療で経過良好症例の組織学的変化の推移を
含めた長期予後に関する検討も，今後の課題
である．

おわりに

診断技術の進歩により AIH の診断数は増
加しているが，同時に従来記載された AIH
典型症例の特徴を具備しない，いわゆる非定
型 AIH の頻度も増加している．典型的 AIH
の根底には多くの非定型症例が存在している
ことも十分あり得ることである．特異的臨床
診断指標が確立していない AIH の診断は，

より困難になっているとも言える．非定型で
かつ軽微な病像を呈する症例の診断，治療方
策，その予後に関する今後の検討が重要であ
る．

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Article

Serial Changes of Serum Growth Factor Levels and Liver Regeneration after Partial Hepatectomy in Healthy Humans

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Abstract: This study aimed to investigate the associations of the serial changes of serum levels of various growth factors with liver regeneration after hepatectomy in healthy liver donors. Sixteen healthy liver donors who underwent conventional liver resection were included. Serum levels of various growth factors before hepatectomy and on postoperative day (POD) 1, 3, 5 and 7 were measured. Liver volume data calculated by multi-detector computed tomography using workstation. The ratio of remnant liver volume on POD 0 to liver volume before the operation was 51% ± 20%. The ratio of liver volume on POD 14 to liver volume on POD 0 were inversely correlated with remnant liver volume on POD 0 ($r = -0.91$). The ratio of liver volume on POD 14 to liver volume on POD 0 were significantly correlated with serum hepatocyte growth factor (HGF) levels on POD 1 ($r = 0.54$), serum leptin levels on POD 1 ($r = 0.54$), and serum macrophage colony-stimulating

factor (M-CSF) levels on POD 5 ($r = 0.76$) and POD 7 ($r = 0.80$). These results suggest that early-phase elevation of serum levels of HGF, leptin and M-CSF may be associated with the acceleration of liver regeneration after hepatectomy in humans.

1. Introduction

Liver transplantation is the only curative treatment for end-stage liver diseases. However, in a setting of the shortage of liver grafts, many patients deteriorate as a result of disease progression or develop complications because of the lack of a timely suitable donor while waiting for a liver graft [1,2]. Thus, in addition to liver transplantation, new therapeutic agents for promoting liver regeneration are desired.

In animal models, the mechanisms of liver regeneration have been investigated in detail. Hepatocytes are primed by tumor necrosis factor (TNF)-α and interleukin (IL)-6 mainly produced by Kupffer cells, and then proliferation and cell growth of hepatocytes are induced in response to transforming growth factor-α, hepatocyte growth factor (HGF), and epidermal growth factor [3]. In addition, vascular endothelial growth factor (VEGF) and thrombopoietin (TPO) are shown to promote liver regeneration [4,5].

In humans, *in vivo* investigations of liver regeneration have been mainly performed in patients undergoing surgical resection of liver cancers or liver transplant recipients; however, underlying diseases and immunosuppressant after liver transplantation may influence liver regeneration. Until now, a few studies have shown that serum HGF and IL-6 levels are elevated on postoperative day (POD) 1 [6–8]. In individuals without the appropriate elevation of serum HGF levels after partial hepatectomy, postoperative liver failure develops more frequently [9]. Serial changes of serum VEGF and TPO levels after partial hepatectomy have been also investigated in healthy liver donors [7,10]. However, associations of these growth factors with liver regeneration have not been fully revealed.

Recently, because of the shortage of liver grafts from deceased donors, the number of living donor liver transplantation has increased. In living donor liver transplantation, healthy liver donors undergo typical and anatomical hepatectomy. So, the mechanisms of liver regeneration in healthy humans, which may be different from those in patients undergoing surgical resection of liver cancers, liver transplant recipients, and animal models, may be revealed. In this study, we investigated the serial changes of serum levels of various growth factors after partial hepatectomy and the associations of these changes of various growth factors with liver regeneration after the operation in healthy liver donors.

2. Results

2.1. Clinical Characteristics of Study Population

Clinical characteristics of 16 healthy liver donors are shown in Table 1. Preoperative liver function tests were within normal limit in all patients. Each donor did not require perioperative transfusion or suffer from any major operative complications after surgery.

Liver graft type and changes of liver volume before and after partial hepatectomy are summarized in Table 2. The ratio of remnant liver volume on POD 0 to liver volume before the operation was 51% ± 20%. The ratio of liver volume on POD 14 to liver volume before the operation was 76% ± 11%. Remnant liver volume per body weight on POD 0 were more in left graft donors than in right graft donors (15.6 ± 1.8 cm^3/kg *versus* 7.7 ± 2.7 cm^3/kg, $p < 0.0001$); however, the ratio of liver volume on POD 14 to liver volume on POD 0 was higher in right liver donors than in left liver donors (199% ± 42% *versus* 114% ± 8%, $p = 0.0003$). Ratio of liver volume on POD 14 to liver volume on POD 0 was inversely correlated with remnant liver volume on POD 0 ($r = -0.91$, $p < 0.0001$) and remnant liver volume per body weight on POD 0 ($r = -0.95$, $p < 0.0001$). On the other hand, the ratio of liver volume on POD 14 to liver volume on POD 0 was not associated with gender, age and body mass index.

Table 1. Clinical characteristics of 16 healthy liver donors on admission.

| Clinical Characteristics	Value
Age (year)	36 ± 12
Gender, female (%)	12 (75)
Height (cm)	161 ± 6
Body weight (kg)	59 ± 11
Body mass index (kg/m^2)	22.8 ± 4.2
Laboratory Data	**Value**
White blood cell count (/mm^3)	5574 ± 890
Hemoglobin concentration (g/dL)	13.4 ± 1.8
Platelet count (×10^4/mm^3)	24.7 ± 3.9
Bilirubin (mg/dL)	0.9 ± 0.5
Albumin (g/dL)	4.5 ± 0.3
Prothrombin time-international normalized ratio (INR)	0.98 ± 0.07
Aspartate aminotransferase (IU/L)	18 ± 4
Alanine aminotransferase (IU/L)	15 ± 9
C-reactive protein (mg/dL)	0.05 ± 0.07

Table 2. Liver graft type and changes of liver volume before and after hepatectomy.

Graft Type	Value
Liver graft type (left graft) n (%)	6 (38)
Liver graft type (right graft) n (%)	10 (62)
Liver volume Change	**Value**
Liver volume before hepatectomy (cm^3)	1213 ± 206
Liver resection rate (%)	49 ± 20
Remnant liver volume on POD 0 (cm^3)	622 ± 262
Remnant liver volume per body weight on POD 0 (cm^3/kg)	10.7 ± 4.6
Liver volume on POD 14 (cm^3)	917 ± 158
Ratio of liver volume on POD 14 to liver volume on POD 0 (%)	167 ± 54

2.2. Postoperative Changes of Laboratory Data and Liver Regeneration

Serial changes of laboratory data before hepatectomy and on POD 1, 3, 5 and 7 are shown in Figure 1.

Figure 1. Serial changes of laboratory data during the clinical course. Laboratory data before hepatectomy and on postoperative day (POD) 1, 3, 5 and 7 were expressed as mean ± standard deviation. Before: before partial hepatectomy; POD: postoperative day; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$; ****: $p < 0.0001$.
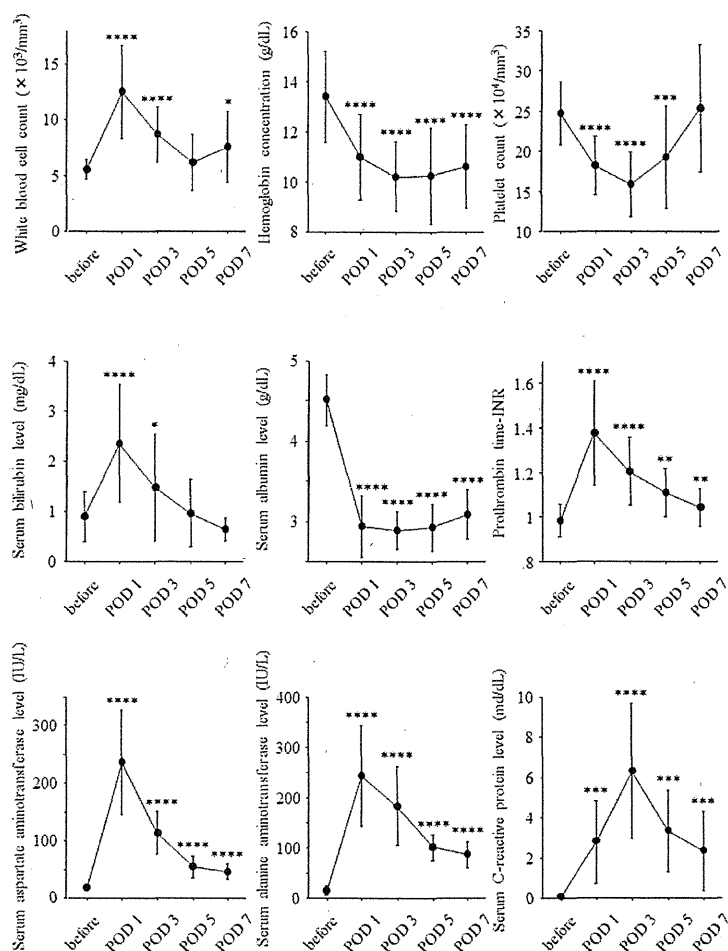

Liver resection rate was significantly correlated with white blood cell counts on POD 1 ($r = 0.65$, $p = 0.005$), serum bilirubin levels on POD 3 ($r = 0.51$, $p = 0.045$), serum albumin levels on POD 3 ($r = 0.57$, $p = 0.020$), serum aspartate aminotransferase levels on POD 3 ($r = 0.63$, $p = 0.007$) and POD 5 ($r = 0.81$, $p = 0.0006$), and prothrombin time-international normalized ratio (INR) on POD 3 ($r = 0.71$, $p = 0.002$) and POD 5 ($r = 0.78$, $p = 0.004$) but was inversely correlated with serum *C*-reactive protein levels ($r = -0.67$, $p = 0.005$). Remnant liver volume per body weight on POD 0 was inversely correlated with white blood cell counts on POD 1 ($r = -0.61$, $p = 0.011$), serum aspartate aminotransferase levels on POD 3 ($r = -0.78$, $p = 0.0002$) and POD 5 ($r = -0.78$, $p = 0.019$), and prothrombin time-INR on POD 3 ($r = -0.68$, $p = 0.003$) and POD 5 ($r = -0.78$, $p = 0.003$) but was significantly correlated with serum C-reactive protein levels ($r = 0.66$, $p = 0.006$).

According to remnant liver volume per body weight on POD 0, 16 patients were divided into two groups. One group consisted of eight patients with remnant liver volume per body weight on POD 0 of 10 cm³/kg or less, and another group consisted of the other eight patients with remnant liver volume per body weight on POD 0 >10 cm³/kg. Serial changes of laboratory data in both the groups

are shown in Figure 2. White blood cell counts on POD 1, serum bilirubin levels on POD 3 and 5, serum albumin levels on POD 3, serum aspartate aminotransferase levels on POD 3 and 5, and prothrombin time-INR on POD 3 and 5 were significantly higher in the eight patients with remnant liver volume per body weight on POD 0 of 10 cm^3/kg or less. On the other hand, serum C-reactive protein levels on POD 1 were lower in this group.

Figure 2. Associations of remnant liver volume per body weight on POD 0 with serial changes of laboratory data during the clinical course. Solid and dotted lines show serial changes of serum levels of each growth factor in eight patients with remnant liver volume per body weight on POD 0 of 10 cm^3/kg or less and the other eight patients with remnant liver volume per body weight on POD 0 > 10 cm^3/kg, respectively. Serum levels of each growth factor before hepatectomy and on POD 1, 3, 5 and 7 were expressed as mean ± standard deviation. Before: before partial hepatectomy; POD: postoperative day; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.
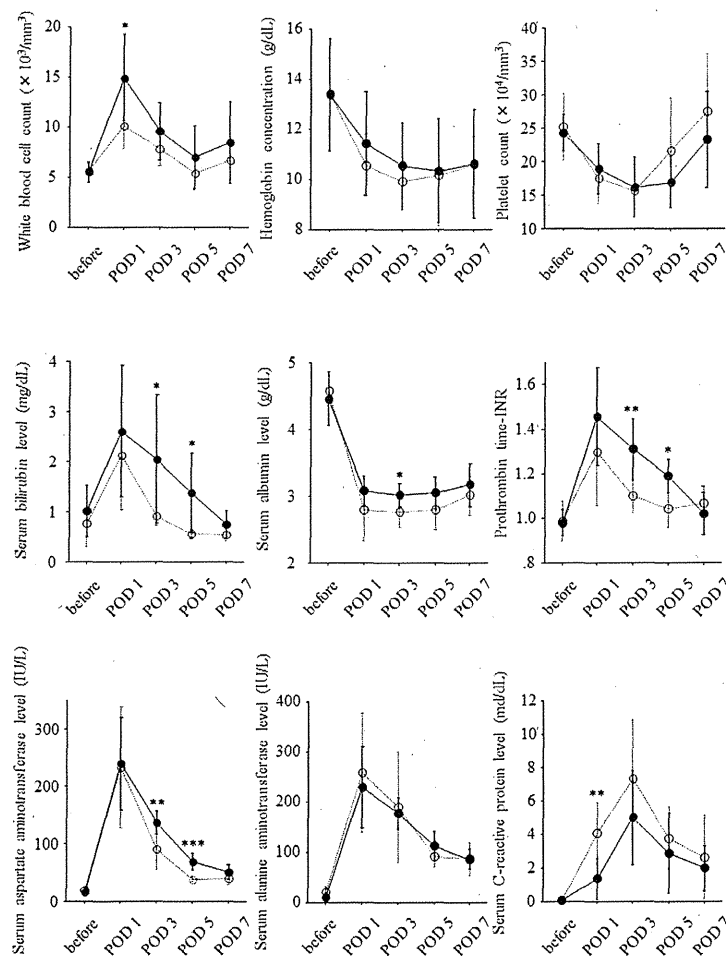
Ratio of liver volume on POD 14 to liver volume on POD 0 was correlated with white blood cell counts on POD 1 ($r = 0.63$, $p = 0.007$), prothrombin time-INR on POD 3 ($r = 0.62$, $p = 0.009$) and POD 5 ($r = 0.72$, $p = 0.010$), and serum aspartate aminotransferase levels on POD 3 ($r = 0.71$, $p = 0.002$) and POD 5 ($r = 0.67$, $p = 0.015$). On the other hand, serum C-reactive protein levels on POD 1 were inversely correlated with ratio of liver volume on POD 14 to liver volume on POD 0 ($r = -0.62$, $p = 0.012$).

According to the ratio of liver volume on POD 14 to liver volume on POD 0, 16 patients were divided into two groups. Eight patients showing ratio of liver volume on POD 14 to liver volume on POD 0 of 150% or higher were classified into high liver regeneration group, and the others eight showing this ratio <150% were classified into low liver regeneration group. Serial changes of laboratory data in both the groups are shown in Figure 3. Prothrombin time-INR on POD 3 and 5, serum bilirubin levels on POD 3 and 7, and serum aspartate aminotransferase levels on POD 3 and 5 were significantly higher in high liver regeneration group. On the other hand, platelet counts on POD 5 and serum C-reactive protein levels on POD 1 were lower in the high liver regeneration group.

Figure 3. Associations of liver regeneration with serial changes of laboratory data during the clinical course. Solid and dotted lines show serial changes of laboratory data in eight patients showing ratio of liver volume on POD 14 to liver volume on POD 0 of 150% or higher and the other eight patients showing this ratio <150%, respectively. Serum levels of each laboratory data before hepatectomy and on POD 1, 3, 5 and 7 were expressed as mean ± standard deviation. Before: before partial hepatectomy; POD: postoperative day; *: $p < 0.05$; **: $p < 0.01$.
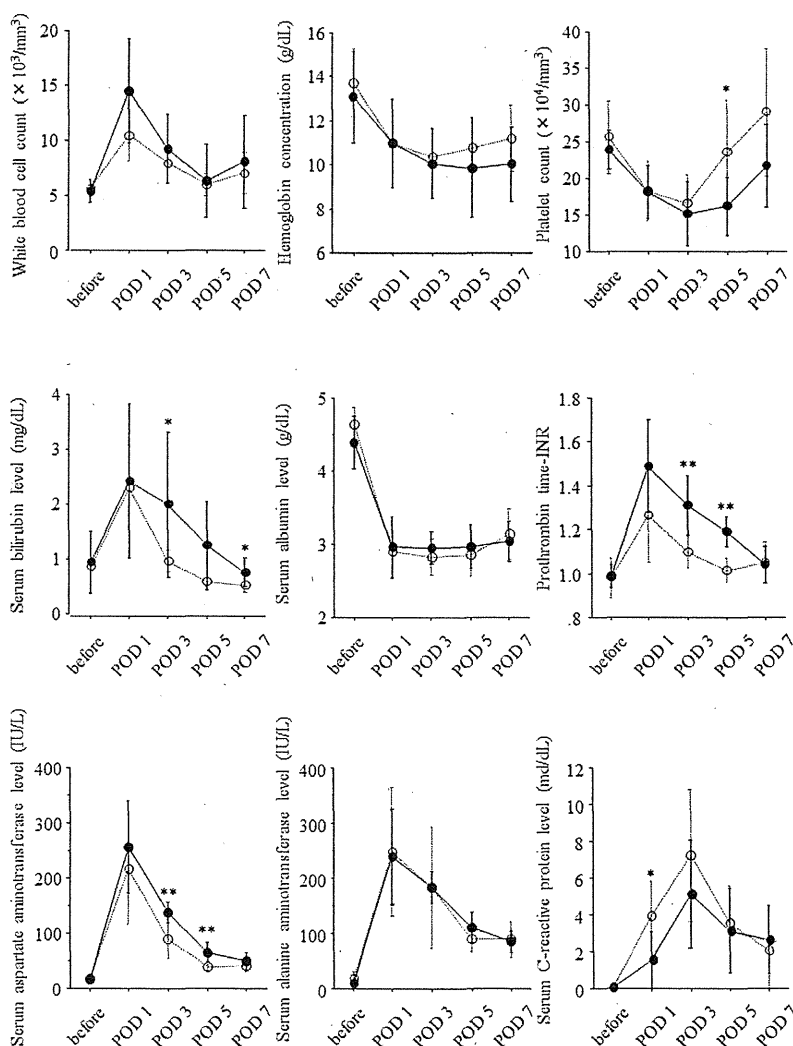
2.3. Postoperative Changes of Serum Growth Factor Levels and Liver Regeneration

Serial changes of serum growth factor levels are shown in Figure 4. Postoperative changes in serum levels of HGF and leptin paralleled those in prothrombin time-INR and serum levels of bilirubin. The changes in serum levels of macrophage colony-stimulating factor (M-CSF) paralleled those in white blood cell counts. The changes in serum platelet-derived growth factor (PDGF)-BB levels paralleled those in platelet counts.

Figure 4. Serial changes of serum levels of nine growth factors during the clinical course. Serum levels of each growth factor before hepatectomy and on POD 1, 3, 5 and 7 were expressed as mean ± standard deviation. Before: before partial hepatectomy; POD: postoperative day; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$; ****: $p < 0.0001$.
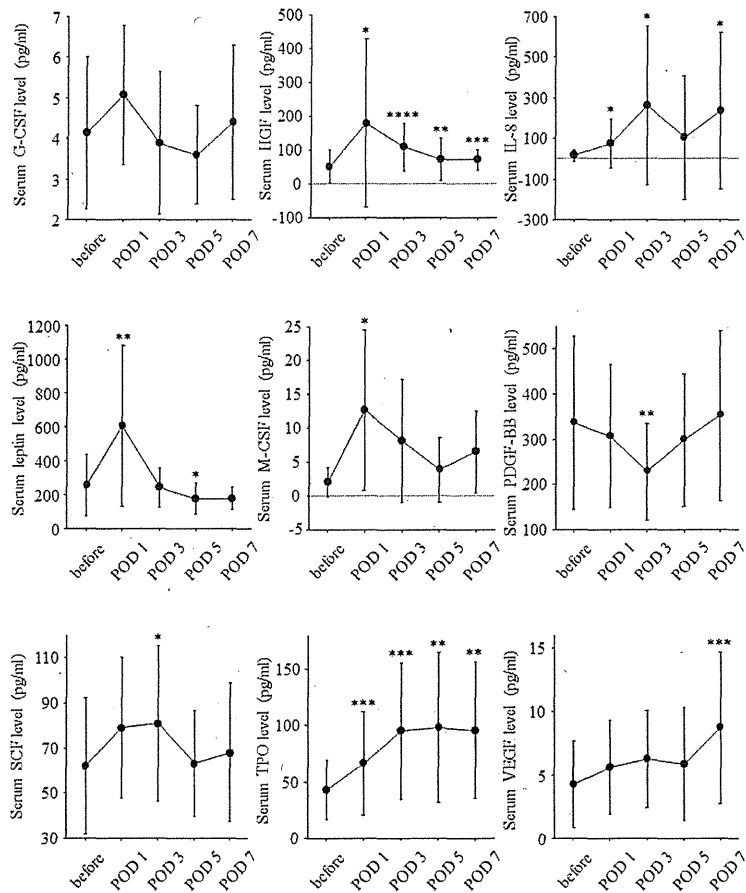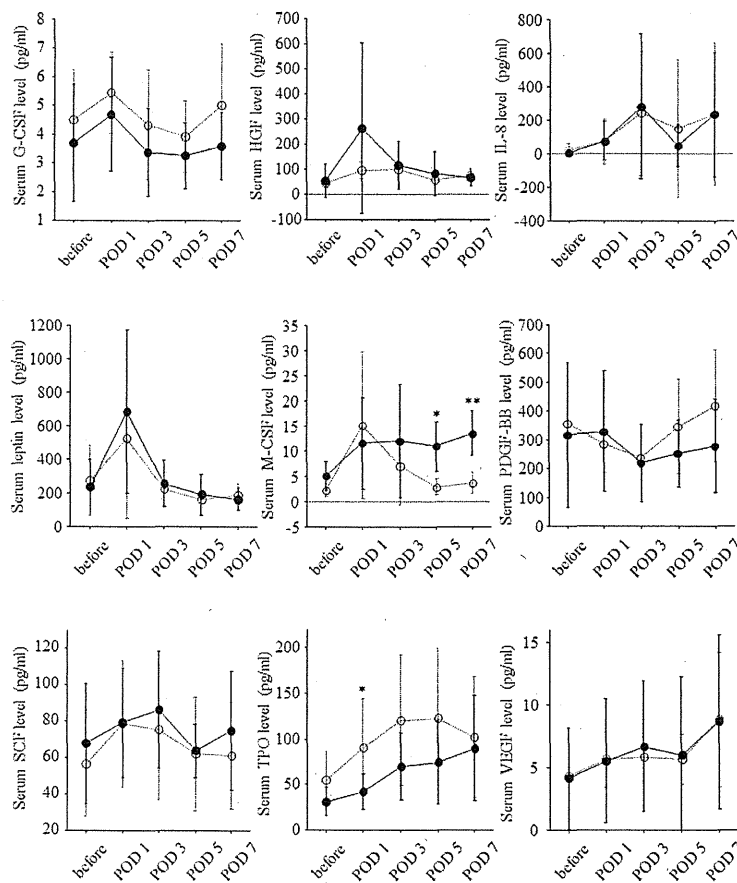

Liver resection rate was significantly correlated with serum M-CSF levels on POD 5 ($r = 0.78$, $p = 0.037$) and POD 7 ($r = 0.81$, $p = 0.003$) but not with serum HGF and leptin levels on POD 1. Remnant liver volume per body weight on POD 0 was inversely correlated with serum M-CSF levels on POD 5 ($r = -0.76$, $p = 0.045$) and POD 7 ($r = -0.75$, $p = 0.010$) and tended to be inversely correlated with serum HGF levels on POD 1 ($r = -0.46$, $p = 0.076$) and serum leptin levels on POD 1 ($r = -0.47$, $p = 0.064$).

According to remnant liver volume per body weight on POD 0, serial changes of serum growth factor levels are shown in Figure 5. In eight patients with remnant liver volume per body weight on

POD 0 of 10 cm³/kg or less, serum M-CSF levels on POD 5 and POD 7 were significantly higher. On the other hand, serum TPO levels on POD 1 were lower in this group.

Figure 5. Associations of remnant liver volume per body weight on POD 0 with serial changes of serum levels of nine growth factors during the clinical course. Solid and dotted lines show serial changes of serum levels of each growth factor in eight patients with remnant liver volume per body weight on POD 0 of 10 cm³/kg or less and the other eight patients with remnant liver volume per body weight on POD 0 >10 cm³/kg, respectively. Serum levels of each growth factor before hepatectomy and on POD 1, 3, 5 and 7 were expressed as mean ± standard deviation. Before: before partial hepatectomy; POD: postoperative day; *: $p < 0.05$; **: $p < 0.01$.


Ratio of liver volume on POD 14 to liver volume on POD 0 was significantly correlated with serum HGF levels on POD 1 ($r = 0.54$, $p = 0.030$), serum leptin levels on POD 1 ($r = 0.54$, $p = 0.028$), and serum M-CSF levels on POD 5 ($r = 0.76$, $p = 0.047$) and POD 7 ($r = 0.80$, $p = 0.003$). On the other hand, ratio of liver volume on POD 14 to liver volume on POD 0 was inversely correlated with serum PDGF-BB levels on POD 5 ($r = -0.61$, $p = 0.011$), and serum TPO levels on POD 1 ($r = -0.60$, $p = 0.012$).

Serial changes of serum growth factor levels in high liver regeneration group and low liver regeneration group are shown in Figure 6. Serum leptin levels on POD 1 and serum M-CSF levels on POD 5 and POD 7 were significantly higher in high liver regeneration group. Serum HGF levels on POD 1 seemed to be higher in high liver regeneration group although the difference was not

significant. On the other hand, serum PDGF-BB levels on POD 5 and serum TPO levels on POD 1 were lower in the high liver regeneration group.

Figure 6. Associations of liver regeneration with serial changes of serum levels of nine growth factors during the clinical course. Solid and dotted lines show serial changes of serum levels of each growth factor in eight patients showing ratio of liver volume on POD 14 to liver volume on POD 0 of 150% or higher and the other eight patients showing this ratio <150%, respectively. Serum levels of each growth factor before hepatectomy and on POD 1, 3, 5 and 7 were expressed as mean ± standard deviation. Before: before partial hepatectomy; POD: postoperative day; $*: p < 0.05$.
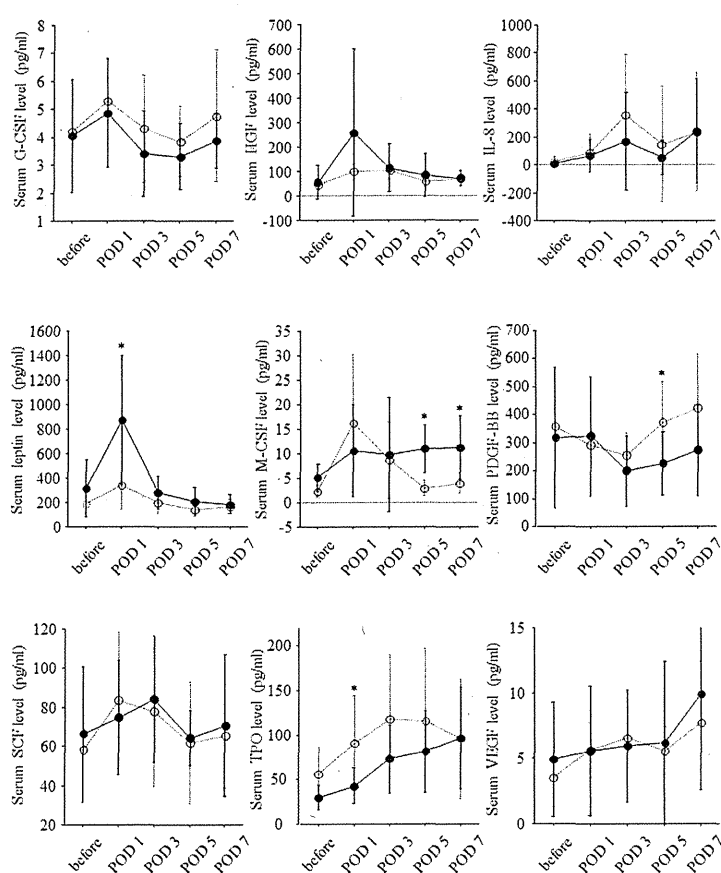
3. Discussion

The liver has strong potential to regenerate. Liver regeneration involves a complex interaction of the proliferation of resident hepatocytes and hepatocyte progenitor cells, the facilitation of angiogenesis, and the differentiation of hematopoietic stem cells into hepatocyte. However, the mechanism of liver regeneration in healthy humans has not been revealed yet. This study indicated that, after partial hepatectomy of the grade not exerting danger on a life, the smaller the remnant liver volume, the higher was liver regeneration, and that various growth factors intricately took parts in liver regeneration after partial hepatectomy. In particular, early-phase elevations of serum levels of HGF, leptin and M-CSF seemed to be associated with the acceleration of liver regeneration after partial hepatectomy.

As is well known, HGF is a potent factor for proliferation of hepatocyte. In this study, serum HGF levels on POD 1 were correlated with ratio of liver volume on POD 14 to liver volume on POD 0. These findings are consistent with the previous reports [6,7]. Recently, a clinical trial using recombinant HGF for acute liver failure has been reported, and it has been shown that intravenous administration of recombinant HGF is well-tolerated [11]. Further clinical trials are required to determine the effect of recombinant HGF on liver regeneration in humans.

Some studies have showed the relation of leptin with liver regeneration in animal models. In leptin-deficient ob/ob mice after toxic liver injury or partial hepatectomy, liver regeneration is impaired with down-regulated hepatic expression of TNF-α and IL-6, and leptin supplementation improves liver regeneration with up-regulated hepatic expression of TNF-α and IL-6 [12,13]. On the other hand, leptin does not directly up-regulate hepatocyte proliferation [14]. Leptin may accelerate liver regeneration through the release of cytokines such as TNF-α and IL-6 from non-parenchymal cells.

M-CSF is produced by non-parenchymal and parenchymal liver cells. In M-CSF-deficient mice, hepatic expressions of TNF-α and IL-6 are reduced, and proliferation of hepatocytes is impaired [15]. On the other hand, in M-CSF-deficient mice, M-CSF supplementation improves liver regeneration [15]. In addition, hepatocyte-like cells are reported to differentiate from peripheral blood monocytes under the stimulation of M-CSF [16]. M-CSF may take a part in liver regeneration through the proliferation of hepatocytes and the differentiation of hematopoietic stem cells into hepatocytes.

An appropriate intra-hepatic inflammatory response to liver injury has been shown to promote liver regeneration [17,18]. In this study, white blood cell counts on POD 1 were correlated with ratio of liver volume on POD 14 to liver volume on POD 0. However, serum *C*-reactive protein levels on POD 1 were shown to be inversely correlated with ratio of liver volume on POD 14 to liver volume on POD 0. This may be partially due to the interaction of *C*-reactive protein with leptin. *C*-reactive protein is reported to inhibit the binding of leptin to its receptor and attenuate its physiological functions [19]. In addition, *C*-reactive protein are shown to induce hepatic insulin-resistance which leads to poor liver regeneration [20,21].

Serum TPO levels in this study were gradually increased after partial hepatectomy, and these changes are consistent with the previous report [10]. TPO promotes liver regeneration after partial hepatectomy [5]. However, in this study, serum TPO levels on POD 1 were correlated with remnant liver volumes on POD 0. TPO is mainly produced by hepatocyte in response to thrombocytopenia when circulating platelet counts is decreased [22]. In this study, platelet counts abruptly decreased after the operation. In response to thrombocytopenia, serum TPO levels after the operation may be elevated in proportion to remnant liver volumes.

4. Materials and Methods

This study was approved by the Institutional Review Board at Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan. Each patient was informed of the nature of the study and signed an informed consent form.

4.1. Study Population

Sixteen healthy liver donors who underwent partial hepatectomy between January 2000 and November 2010 were prospectively included in this study. Eight donors underwent a right lobectomy, three did an extended left lobectomy, two did a left lateral segmentectomy, one did a left lobectomy, and two did a right posterior segmentectomy, respectively.

4.2. Measurement of Serum Growth Factor Level

Sera were collected prior to the operation and on POD 1, 3, 5 and 7. Samples were frozen and stored at −80 °C until analysis.

Serum levels of the following growth factors were measured using the Bio-Plex Protein Array System (Bio-Rad Laboratories, Hercules, CA, USA): granulocyte colony-stimulating factor, HGF, IL-8, leptin, M-CSF, PDGF-BB, stem cell factor, and VEGF. In brief, the Bio-Plex Pro Standard and samples diluted in Serum Diluent were added to a 96-well filter plate and incubated with the antibody-coupled beads for 1 h with continuous shaking. The beads were washed three times with wash buffer to remove unbound protein and incubated with biotinylated detection antibodies for 30 min with continuous shaking. Following three washes, premixed streptavidin-phycoerythrin was added to each well and incubated for 30 min. After incubation, the beads were washed and re-suspended in assay buffer. The reaction mixture was quantified using the Bio-Plex protein array reader. Each growth factor level was automatically calculated by Bio-Plex Manager software using the appropriate standard curve.

Serum TPO level was measured using an enzyme-linked immunosorbent assay kit according to the manufacturer's instructions (Quantikine Human TPO Immunoassay, R&D Systems, Minneapolis, MN, USA). Microplates were coated with manufacturer-provided monoclonal antibodies against TPO, and following the enzyme reaction the plates were measured using a microplate manager (BIO-RAD Laboratories, Hercules, CA, USA) and the optical density was determined at 450 nm.

4.3. Volumetric Study of Liver

Liver volumes were measured by multi-detector computed tomography (Aquilion 64, Toshiba Medical Systems Corporation, Otowara, Japan) using workstation (Virtual Place Advance Plus, Aze, Tokyo, Japan).

The liver resection rate (%) was calculated as follows: resected liver graft volume (cm^3)/liver volume before the operation (cm^3) × 100%.

4.4. Statistical Analysis

SPSS statistical program (release 11.0.1 J, SPSS, Chicago, IL, USA) was used for the statistical analysis.

Dichotomous variables were compared by the chi-squared test. Continuous variables were expressed as mean ± standard deviation (SD). Student's *t*-test was used to evaluate differences in the continuous variables between two groups. The Pearson's correlation test was used to evaluate the consistency in the continuous variables between two groups. *p*-values < 0.05 were considered significant.

5. Conclusions

After partial hepatectomy of the grade not exerting danger on a life, the smaller the remnant liver volume, the higher the liver regeneration is. This study indicates that various growth factors are associated with liver regeneration after partial hepatectomy in healthy humans. In particular, early-phase elevation of serum levels of HGF, leptin and M-CSF may be associated with accelerated liver regeneration. HGF, leptin and M-CSF possibly become new therapeutic agents for promoting liver regeneration. In addition, serial changes of serum levels of these growth factors may be early predictors of liver regeneration after hepatectomy. In order to confirm these findings in healthy humans, further studies are required.

Conflicts of Interest

The authors declare no conflict of interest.

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自己免疫性肝炎における新規自己抗体

みやけ　やすひろ　　まつもと　かずゆき　　おおにし　あつゆき
三宅 康広　　松本 和幸　　大西 敦之
まつした　ひろし　　たかき　あきのぶ　　やまもと　かずひで
松下 浩志　　高木 章乃夫　　山本 和秀

岡山大学病院　消化器内科

要　　旨：抑制性の補助刺激分子 programmed cell death-1(PD-1)に対する血清中抗体価を間接ELISA
法で測定した。抗PD-1抗体価は，薬物性肝障害(DILI)群や急性ウイルス性肝炎群，健常者
群に比べて自己免疫性肝炎(AIH)群で高値であった。また，AIH群では，抗PD-1抗体価と
ビリルビンやトランスアミナーゼが正に相関しており，抗PD-1抗体陽性例では陰性例に比
べて抗核抗体の陽性率が高かった。血清中抗PD-1抗体は，AIHとDILIの鑑別に有用であ
り，AIHの病態に関与している可能性が推測される。　　【消化器と免疫49(2012)3-6】

Key words ：自己免疫性肝炎；薬物性肝障害；診断；補助刺激分子；PD-1

はじめに

自己免疫性肝炎(AIH)は，血清中での自己抗体出現や高ガンマグロブリン血症，肝組織中での門脈域へのリンパ球や形質細胞浸潤，interface hepatitis を特徴とする慢性炎症性肝疾患である[1]。AIH の診断は，gold standard が存在しないために各種診断基準によって行われており，血清中の抗核抗体と免疫グロブリン G (IgG) 値，肝組織所見が主要な評価項目となっている[2,3]。しかし，最近我が国で行われた全国調査結果により，AIH 患者の26％で抗核抗体が陰性または40倍と低力価であることや39％でIgG 値が2 g/dl 以下であることが示された[4]。また，我が国で一般人口を対象に行われた研究では，女性の32％が40倍以上の抗核抗体陽性を示すことが報告されている[5]。抗核抗体陰性例やIgG 値が正常値を示す非典型

例の増加が明らかとなった今，AIH の診断に有用なバイオマーカーの特定が熱望される。

最近，活性化状態の T 細胞表面に発現される抑制性の補助刺激分子 programmed cell death-1 (PD-1) をノックアウトしたマウスで生後3日目に胸腺摘出を行うと，血清中に抗核抗体が出現しAIH 様の肝病変が出現すると報告された[6]。また，抗悪性腫瘍剤としてヒトに抗 PD-1 抗体を投与する臨床試験では，一部の症例でステロイドホルモン剤の著効する肝炎が副作用として報告されている[7]。通常，定常状態にある T 細胞表面には補助刺激分子である CD28 が発現しており，抗原提示細胞上のリガンドと反応することで T 細胞が活性化される。一方，活性化状態にある T 細胞表面には抑制性の補助刺激分子である CTLA4 や PD-1 が発現しており，これらが抗原提示細胞上のリガンドと反応することで T 細胞