表1　E型急性重症肝炎例(岩手医科大学第一内科)

| | 症例1 | 症例2 | 症例3 | 症例4 | 症例5 | 症例6 |
|---|---|---|---|---|---|---|
| 性・年齢(歳) | 男・61 | 男・60 | 女・65 | 女・59 | 女・54 | 男・65 |
| 職業 | 塗装店経営 | 会社経営 | 主婦 | 精肉加工業 | 主婦 | 左官業 |
| 生活歴 | | | | | | |
| 海外渡航歴(1年以内) | 無 | 無 | 無 | 無 | 無 | 無 |
| 井戸水摂取(3カ月以内) | 無 | 無 | 無 | 無 | 無 | 無 |
| 生の海産物摂取(3カ月以内) | 無 | 無 | 無 | 無 | 無 | 無 |
| 動物との摂食(3カ月以内) | 無 | 無 | 無 | 無 | 無 | 無 |
| 薬剤の内服 | 無 | 無 | 有 | 有 | 無 | 有 |
| 臨床症状 | | | | | | |
| 発熱(＞38℃) | 無 | 無 | 無 | 無 | 有 | 無 |
| 感冒様症状 | 有 | 有 | 無 | 無 | 有 | 有 |
| 全身倦怠感 | 有 | 有 | 有 | 有 | 無 | 無 |
| 下痢症状 | 無 | 有 | 無 | 無 | 有 | 無 |
| 食欲不振・嘔気・嘔吐 | 有 | 有 | 無 | 有 | 無 | 無 |
| 発生年度 | 1993 | 1995 | 2001 | 2002 | 2004 | 2004 |
| 臨床病型 | 劇症肝炎 | 劇症肝炎 | 遅発性肝不全 | 亜急性肝炎 | 急性肝炎重症型 | 急性肝炎(HEV＋薬剤) |
| T.Bil (mg/dl) | 23.5 | 35.0 | 36.0 | 28.1 | 6.4 | 30.4 |
| AST (IU/L) | 184 | 2,276 | 1,965 | 1,458 | 2,380 | 1,548 |
| ALT (IU/L) | 572 | 2,256 | 2,153 | 819 | 692 | 1,483 |
| PT (%) | 6 | 13 | 9 | 24 | 38 | 79 |
| HEV genotype | IV | III | III | III | III | III |
| 転帰 | 死亡 | 死亡 | 死亡 | 生存 | 生存 | 死亡 |
| 関連事項 | | | 発症前薬剤服用あり | DLST陽性 | | 薬剤過敏性症候群, DIC |

1993～2004.9まで

他施設の報告では，相川の報告例(1998年)[4,20]は66歳の男性で，劇症肝炎亜急性型の経過をたどり死亡しており，遺伝子型はIV型である．Yazakiら[8]の報告した2例は，いずれも中高齢者の男性(64歳，58歳)で，それぞれ急性型および亜急性型の経過で死亡しているが，遺伝子型はいずれもIV型であった．さらに，Ohnishiら[17]は2例のE型劇症肝炎例を報告しているが，1例は34歳の女性，他の1例は51歳の男性であり，いずれも亜急性型の経過をたどり死亡している(女性の1例は生体肝移植後に死亡)．遺伝子型はそれぞれIII型，IV型であった．また，三浦ら[21]は腸チフスによる敗血症を併発したE型急性肝炎の1例(22歳，男性，海外渡航歴あり)を報告しているが，重症化についてはHEVそのものに起因するのか，あるいは薬剤などの他の要因や合併症が関与しているのかは明らかでない．最近，Mizuoら[22]は北海道地域で経験した重症E型肝炎の臨床像と遺伝子型を検討し，遺伝子型IV型はIII型に比べて血清トランスアミナーゼのピーク値が有意に高く，一方，プロトロンビン時間(PT)のピーク値は有意に低いことを報告し，遺伝子型の違いが肝炎の重症度に関係する可能性を報告している．

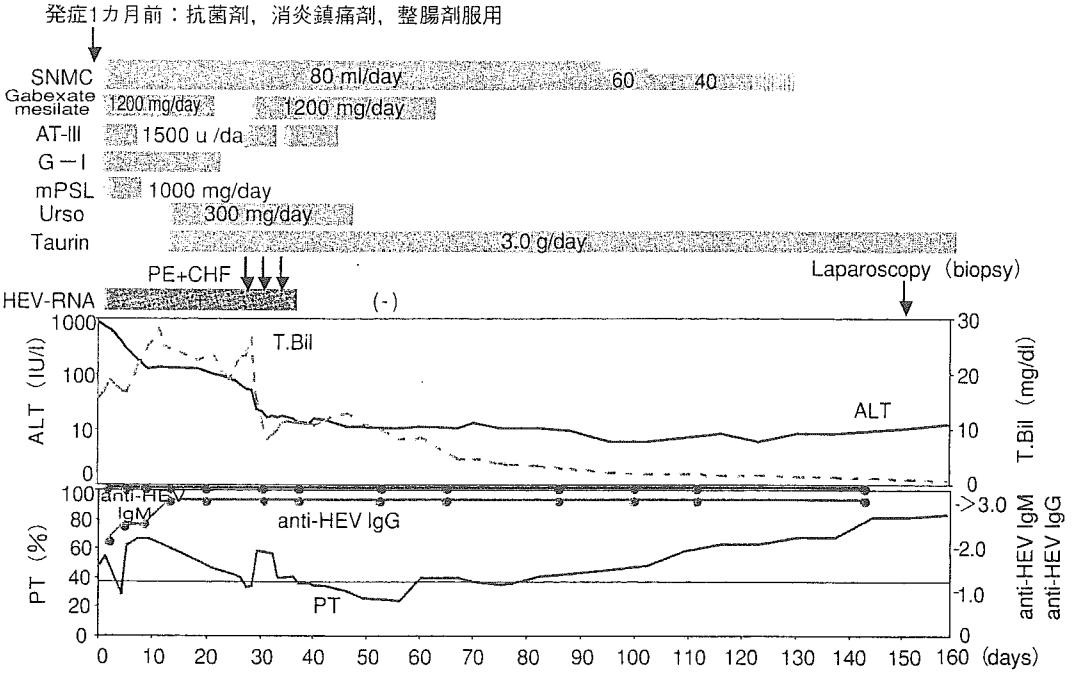


図2　症例4（59歳，女性，亜急性肝炎）臨床経過

以下に，薬剤性肝障害にE型肝炎を合併し重症化した1症例を示す．

症例は59歳，女性（表1の症例4）で，図2に臨床経過を示した．既往歴に46歳時のB型急性肝炎，55歳時の高血圧を指摘されている．魚介類の生食，湧き水の摂取があり，職業は精肉加工業であったが，これらとの関連性を示す証拠は得られなかった．海外渡航歴はなく，動物との接触，飲酒歴，喫煙歴はなかった．平成14年（2002年）1月15日に歯科医院で歯科治療を受け，同院で処方された抗菌剤，消炎鎮痛剤，整腸剤の3種類を3日間内服し，2月8日にも同院で同歯科治療を受け，同薬を2日間内服した．同日より全身倦怠感，食欲不振，尿濃染を自覚していたが放置．2月12日に眼球黄染を自覚し，2月13日に近医を受診．採血で，黄疸，肝機能障害を認めたため当科紹介入院となった．入院時検査所見上，T.Bil 15,2 mg/dl，AST 1,458 IU/l，ALT 819 IU/lと高度の黄疸と肝機能値異常を認め，PTは49％と低下していた．各種ウイルスマーカーでは，HBVの既感染を示す所見およびTTV陽性以外は異常所見を認めなかった．各種薬剤のDLSTでは，消炎鎮痛剤と整腸剤が陽性を示した（表2）．入院当初，肝庇護剤（強力ネオミノファーゲンC：SNMC），抗凝固療法（Gabexate mesilate，AT-Ⅲ），グルカゴン－インスリン（G-I）療法，ステロイド（mPSL）療法を施行し，血清トランスアミナーゼ値は低下したが，黄疸が遷延したためウルソ，タウリンの内服を開始した．しかし，PTの低下傾向と，腹水の増悪傾向を認めたため，血漿交換（PE）と血液濾過透析（CHF）を3日間施行した．その後，徐々にではあったが軽快し，第161病日に退院した．入院時保存血清および経時的な保存血清のHEV検討により40日間HEV-RNA陽性を示し，遺伝子型はⅢ型であった．症状軽

表2　入院時血液検査成績(症例4)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Hematology | | | BUN | 10.5 | mg/dl | anti- HBc | 99.9 | % |
| WBC | 5,200 | / μ l | CRNN | 0.7 | mg/dl | anti- HBc × 200 | 19.6 | % |
| Neutrophil | 64.1 | % | Na | 139 | mEq/l | HBV (realtimePCR) | | |
| Lymphocyte | 22.0 | % | K | 3.9 | mEq/l | | $< 2.0 \times 10^2$ | COPY/mL |
| Monocyte | 9.4 | % | Cl | 107 | mEq/l | anti-HCV | 0.2 | C.O.I. |
| Eosinophil | 0.5 | % | | | | EBV.VCA IgM | < × 10 | |
| Basophil | 0.2 | % | Coagulation tests | | | EBV.VCA IgG | × 320 | |
| RBC | 420 | $\times 10^4$/ μ l | APTT | 29.6 | sec | EBV.EBNA | × 40 | |
| Hb | 13.5 | g/dl | PT | 13.9 | sec | CMV IgM | < × 10 | |
| PLT | 19.7 | $\times 10^4$/ μ l | | 49 | % | CMV IgG | × 40 | |
| | | | HPT | 42.1 | % | パルボB19 IgM | 0.19 | |
| Blood Chemistory | | | Fbg | 221.3 | mg/dl | パルボB19 IgG | 6.15 | |
| T.P. | 6.6 | g/dl | FDP | 3.1 | μ g/ml | TTV-DNA | (+) | |
| Alb | 3.0 | g/dl | D-dimer | 1.4 | μ g/ml | HEV RNA | (+) | |
| T.Bil. | 15.2 | mg/dl | | | | anti-HEV IgM | > 3.0 | |
| D.Bil. | 12.1 | mg/dl | Auto-antibodies | | | anti-HEV IgG | 2.111 | |
| AST | 1,458 | IU/l | ANA | (−) | | | | |
| ALT | 819 | IU/l | AMA | (−) | | Others | | |
| LDH | 519 | IU/l | AMA-$M_2$ | (−) | | hHGF | 2.49 | ng/ml |
| Al-P | 652 | IU/l | ASMA | (−) | | AFP | 6.8 | ng/ml |
| γ -GTP | 389 | IU/l | | | | CD 4/8 | 1.29 | |
| ChE | 206 | IU/l | Viral markers | | | DLST: 消炎鎮痛剤 | | |
| TC | 175 | mg/dl | IgM HA Ab | 0.1 | C.O.I. | | (371 S.I.%) | |
| TBA | 263.2 | μ M/l | IgM-HBc Ab | 0.2 | C.O.I. | 整腸剤 | | |
| IgG | 1,698 | mg/dl | HBs-Ag | 0.0 | C.O.I. | | (807 S.I.%) | |
| IgA | 578 | mg/dl | anti- HBs | 13.7 | C.O.I. | Ⅳ型collagen | 400 | ng/ml |
| IgM | 176 | mg/dl | HBe-Ag | 0.0 | C.O.I. | HYA | 824 | ng/ml |
| $NH_3$ | 96 | μ g/dl | anti-HBe | 79.4 | % | | | |

図3　腹腔鏡像(症例4)
左葉

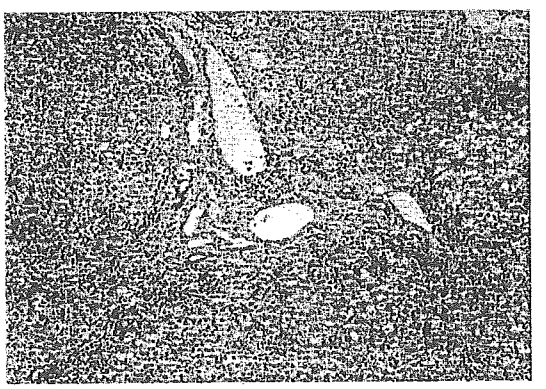

図4　肝組織像(症例4)
H-E stain (× 100)

快後，腹腔鏡下肝生検を施行したが，腹腔鏡像では肝臓の辺縁は両葉とも鈍化，左葉は肥大，右葉は萎縮し，肝表面は区域化がみられた．血管増生，白色紋理をびまん性に認め，島田の分類300.10.4.番に相当する所見であった(図3)．生検標本では，門脈域に炎症細胞浸潤と細胆管の増生，門脈域辺縁にはpiecemeal necrosisがみられ，focal necrosisも認めた．門脈域は線維性の拡大をしており，bridging fibrosisがみられ，一部で実質域の辺縁は丸みを帯びており，小葉構造のひずみが示唆された．一部ではpericellular fibrosisをみた．過去に感染したHBVが関与したかどうかは不明であった(図4)．

## 4 おわりに

E型肝炎の重症例について自験例を中心に解説した．E型急性肝炎は，一般に，男性かつ高齢の飲酒者が多く，重症化には遺伝子型Ⅳ型が関わる可能性が高い．また，当科の重症化例の経験から薬剤などの関与も考えられる．今後，E型肝炎は増加することも予想されることから，血清学的な診断法の確立や感染経路の解明，ウイルス学的な解析，病態の実態調査などさらなる検討を要すると考えられる．また，日常の臨床の現場では，急性肝炎の原因の一つとして，HEVの関与も常に念頭におきながら，病歴聴取などを行う必要があると思われる．

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〔お知らせ〕

## 第16回　腹腔鏡的治療研究会

会　期：2005年11月19日（土曜）
会　場：アキタパークホテル
〒010–0951 秋田市山王4–5–10（電話018–862–1515）（秋田駅より車で10分）
会　長：小松寛治（本荘第一病院）
特別講演：東北大学教授（先進医工学研究機構）
東北大学病院移植・再建・内視鏡外科　黒川良望先生
演題募集：
主題
1. 肝癌に対する腹腔鏡的局所治療
2. 胆嚢・胆道良性疾患に対する腹腔鏡下治療
3. 腹部救急における腹腔鏡診断と治療
4. 胃癌に対する腹腔鏡下手術
5. 大腸癌に対する腹腔鏡下手術
6. 婦人科疾患における腹腔鏡下手術
7. 泌尿器科疾患における腹腔鏡下手術
8. 乳腺の内視鏡下手術
9. 甲状腺・副甲状腺の内視鏡下手術
その他　腹腔鏡に関する演題を広く募集します．
演題募集締め切り：2005年9月9日（必着）
申込先：本荘第一病院
第16回腹腔鏡的治療研究会　会長　小松寛治（事務局担当：鈴木克彦）
〒015–8567 秋田県由利本荘市岩渕下110
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# 重症肝炎との関連性濃厚なE型肝炎ウイルスgenotype IV内の広域分布型一系統：鳥取，新潟，札幌から得られた3本の完全長および1本の準完全長HEV塩基配列

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大西　幸代　　豊田　成司　　山際　　訓　　前久保博士　　安倍　夏生　　三代　俊治

「肝臓」第46巻　第6号（2005）別刷

＜短　報＞

# 重症肝炎との関連性濃厚なE型肝炎ウイルスgenotype IV内の広域分布型一系統：鳥取，新潟，札幌から得られた3本の完全長および1本の準完全長HEV塩基配列

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**緒言**：感染症の重症化には宿主側因子と病原体側因子の両者が関与している．稀ながら発生する劇症E型肝炎には従前専ら前者（妊娠など）が強調されてきたが，HEV側因子の関与する可能性も閑却してはならない．新規に得られた3本の完全長及び1本の準完全長HEV塩基配列を基に，その可能性を探った．

**対象と方法**：2003年に鳥取県で経験されたE型劇症肝炎患者（"Patient B" in Matsuda et al[1]）由来のHEV部分塩基配列は，新潟県及び北海道の2名の急性肝炎（AH）及び1名の劇症肝炎（FH）由来のそれに類似していたので，以上4本のHEV株の塩基配列を完全長化することを試み，相互比較すると同時に，既報株配列との比較を行った．

**成績**：上記4株は相互に99.5%以上の塩基配列一致度を示し，同一系統株であることが示唆された．既報株との比較の為にORF1及びORF2の部分塩基配列を以てデータベースを検索したところ，上記4株を含む9株（うち1株はブタ由来）が，genotype IV内の同一クラスターの中に入ることが判明した（Fig. 1）．このクラスターの特徴は2点存在した．第一には，北海道，茨城，栃木，新潟，鳥取と，日本列島を縦断するかの如く広域に分布している点である（因みに今一つのクラスターは札幌の『地ビールス』である）．第二の特徴は臨床病型であって，Table 1に示す如く，このクラスター内の株に感染した9名の内の3名がFH，1名が急性肝炎重症型（ASH），残りの5名はAHと診断されてはいたが，内2名はプロトロンビン時間が39.7%と44%であった．総ビリルビン値が10 mg/dl以下を示した患者は1名のみである（2名は不明）．

**考案**：自験例に報告例を加えて解析した結果，HEV genotype IV内の或る特定のストレインが，FH，ASH，及び比較的重症のAHと濃厚に関連している可能性が示唆された．解析対象臨床データに幾つかの欠落があった（Table 1）ことが残念であるが，更なる症例の集積によって病原体・病型相関への認識が深化することを期待する．本ストレインが日本列島上に広域分布することの理由は定かでないが，採取時期がわかっており且つ99.5%以上の塩基配列一致度をもつ5株を時間軸に沿って並べると，JYN-Sap 01C（2001. 12. 28札幌），JSN-Sap-FH02C（2002. 3. 21札幌），HE-JK4（2002. 4. 25栃木），JYN-Nii02L（2002. 4. 30新潟），JSF-Tot03C（2003. 3. 12鳥取）の順序となり，恰も日本列島を東から西へと本ストレインが伝播範囲を次第に拡大してきたかのようにも見える．だとすれば，何がこのストレインの主たる『運び屋』だったのか？

**索引用語**：E型肝炎，劇症肝炎，重症化因子，genotype IV，virulent strain

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**Table 1**　Patients infected with the HEV isolates of the concerned lineage within genotype IV

| Case | HEV isolate | Length, Accession no. | Reference | Habitat | TB[a] (mg/dl) | PT[b] (%) | Diagnosis[c] |
|---|---|---|---|---|---|---|---|
| A | (JSF-Tot03C)[d] | | 1) | Tottori | 10.2 | 17 | ASH |
| B | JSF-Tot03C | 7251, AB193176 | 1) & this study | Tottori | 17.1 | 40 | FH |
| SN | JSN-Sap-FH02C | 7251, AB200239 | 2) & this study | Sapporo | 12.2 | 25 | FH |
| YNi | JYN-Sap01C | 7256, AB193177 | This study | Sapporo | 10.0 | 44 | AH |
| YNo | JYN-Nii 02 L | 7154, AB193178 | This study | Niigata | U[e] | U | AH |
| JK4 | HE-JK4 | 7250, AB099347 | 3) | Tochigi | 33.0 | 39.7 | AH |
| JI4 | HE-JI4 | 7186, AB080575 | 4) | Tochigi | 10.1 | U | AH |
| JF3 | HE-JF3 | 412, AB079764 | 5) | Ibaraki | U | U | FH |
| JA1 | HE-JA1 | 7258, AB097812 | 6) | Sapporo | 4.2 | U | AH |

[a] Total bilirubin. [b] Prothrombin time. [c] ASH: acute severe hepatitis; FH: fulminant hepatitis; AH: acute hepatitis. [d] Patient A was exposed to the same infection source as the patient B. [e] Data unavailable.

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＜受付日2005年2月2日＞＜採択日2005年4月28日＞

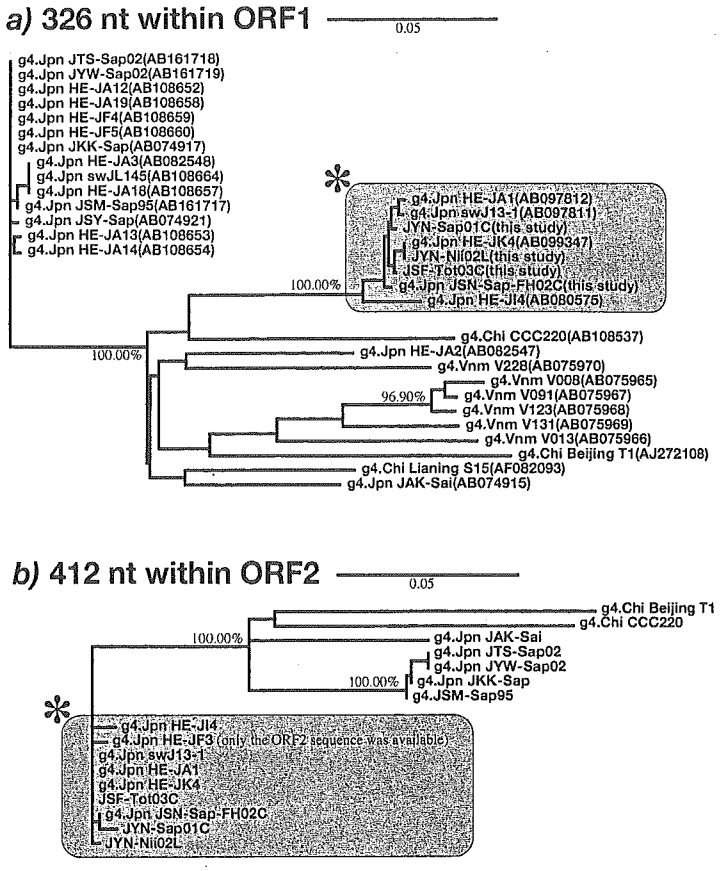


**Fig. 1**　Phylogenetic trees by NJ methods：a) Based on a partial sequence within ORF 1, and b) ORF 2. Only genotype IV isolates are shown. The cluster of HEV concerned in this study is shaded.

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## 英文要旨

### A lineage of hepatitis E virus within genotype IV, associated with severe forms of hepatitis

Takahashi K [1], Okada K [2], Kang JH [3], Karino Y [4], Ichida T [5], Matsuda H [6], Ohnishi S [3], Toyota J [4], Yamagiwa S [5], Maekubo H [3], Abe N [1], Mishiro S [1]*

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We found a lineage of hepatitis E virus (HEV) within genotype IV, members of which were JSF-Tot03C, JSN-Sap-FH02C, JYN-Sap 01C, HE-JK4, JYN-Nii 02L, HE-JF3, HE-JA 1, HE-JI4 from humans and swJ13-1 from swine, all from Japan. Interestingly, of 9 patients infected with the HEV of this lineage, 3 were with fulminant hepatitis, and another 3 were with considerably prolonged prothrombin time (17%, 40% and 44%). In addition, at least 6 patients showed bilirubin levels greater than 10 mg/dl. Although host factors (pregnancy for example) may contribute much to clinical phenotypes of HEV infections, our present results suggest that a viral factor may also play an important role therein.

*Kanzo* 2005；46：389—390

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# Possible Risk Factors for the Transmission of Hepatitis E Virus and for the Severe Form of Hepatitis E Acquired Locally in Hokkaido, Japan

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Hepatitis E in industrialized countries has not been well studied. To define the possible risk factors for transmission of hepatitis E virus (HEV) and for the severe form of hepatitis E in Japan, we investigated the clinical and virological characteristics of hepatitis E in 32 patients who contracted the mild (n = 23) or severe form (n = 9) of domestically acquired hepatitis E between 1996 and 2004 in Hokkaido, where hepatitis E is most prevalent in Japan. Nine patients with the severe form of hepatitis E included two patients with fulminant hepatitis E and seven patients who were diagnosed with severe acute hepatitis in which hepatic encephalopathy did not appear during the course of the illness despite low plasma prothrombin activity (≤40%) and/or increased total bilirubin level (≥20 mg/dl). At least 25 patients (78%) had consumed uncooked or undercooked pig liver and/or intestine 1–2 months before the onset of hepatitis E. When compared with the seven patients with HEV genotype 3, the 25 patients with HEV genotype 4 had a higher peak alanine aminotransferase (ALT) level ($P = 0.0338$) and a lower level of lowest prothrombin activity ($P = 0.0340$). The severe form of hepatitis E was associated with the presence of an underlying disease (56% [5/9] vs. 17% [4/23], $P = 0.0454$). The study suggests that zoonotic food-borne transmission of HEV plays an important role in the occurrence of hepatitis E in Hokkaido, Japan, and that the HEV genotype and the presence of an underlying disease influence the severity of hepatitis E. ***J. Med. Virol. 76:341–349, 2005.*** © 2005 Wiley-Liss, Inc.

**KEY WORDS:** hepatitis E; hepatitis E virus; fulminant hepatitis; genotype; risk factors; zoonosis



## INTRODUCTION

Hepatitis E virus (HEV) is a major cause of enterically transmitted non-A and B-hepatitis in many developing countries where sanitation is suboptimal [Purcell and Emerson, 2001]. Besides imported cases of hepatitis E, domestically acquired hepatitis E has been reported recently in many industrialized countries including the United States, European countries, and Japan [Harrison, 1999; Purcell and Emerson, 2001; Schlauder and Mushahwar, 2001; Smith, 2001; Okamoto et al., 2003]. HEV was classified recently as the sole member of the genus *Hepevirus* in the family *Hepeviridae*. Its genome is a single-stranded, positive-sense RNA of approximately 7.2 kb, with three partially overlapping open reading frames (ORFs: ORF1, ORF2, and ORF3) [Reyes et al., 1990; Tam et al., 1991; Huang et al., 1992; Wang et al., 2000].

Based on the extensive genomic variability noted among HEV isolates, HEV sequences have been classified into four genotypes (genotypes 1–4). The majority of HEV infections in developing countries in Asia and Africa are caused by genotype 1; one epidemic of infection with HEV of genotype 2 has been documented

The nucleotide sequence data reported in this study have been assigned DDBJ/EMBL/GenBank accession numbers AB194282-AB194299.

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in Mexico; and infection with HEV of genotype 3 or 4 has been described in several industrialized countries [Schlauder and Mushahwar, 2001]. There is also evidence that some animals, particularly swine, may act as reservoirs of HEV [Meng et al., 1997, 1998; Erker et al., 1999; Harrison, 1999; Okamoto et al., 2001; Smith, 2001; He et al., 2002; Meng, 2003; Nishizawa et al., 2003; Tei et al., 2003; Yazaki et al., 2003]. Numerous strains of HEV of genotype 3 or 4 have been isolated from pigs in both developing and industrialized countries [Meng et al., 1997; Hsieh et al., 1999; Pina et al., 2000; Garkavenko et al., 2001; Okamoto et al., 2001; van der Poel et al., 2001; Arankalle et al., 2002; Huang et al., 2002; Pei and Yoo, 2002; Wang et al., 2002; Choi et al., 2003; Takahashi et al., 2003].

It has been shown that polyphyletic HEV strains of genotypes 3 and 4 are circulating in Japan [Mizuo et al., 2002; Takahashi et al., 2002a,b] and that the cause of several cases of hepatitis E in Japan can be traced to zoonotic food-borne transmission of HEV from pigs, wild deer or boars to humans [Matsuda et al., 2003; Tei et al., 2003; Yazaki et al., 2003; Tamada et al., 2004]. Furthermore, Japanese patients with severe or fulminant hepatitis E who had never been abroad have been reported [Suzuki et al., 2002; Ohnishi et al., 2003; Yazaki et al., 2003; Kato et al., 2004]. However, the mode of HEV transmission remains unclear in the majority of cases with sporadic acute or fulminant hepatitis E in Japan, and risk factors for the development of severe or fulminant hepatitis E are unknown. Therefore, in the present study, we investigated the clinical and virological characteristics of locally acquired hepatitis E in 32 patients in Hokkaido where acute autochthonous hepatitis E is most prevalent in Japan, in an attempt to elucidate the risk factors for the transmission of HEV and risk factors for the severe form of hepatitis E.

## MATERIALS AND METHODS

### Patients

A total of 32 patients (26 men and 6 women; age, 56.6 ± 14.5 [mean ± standard deviation, SD], [range, 25–86] years) were diagnosed with clinical HEV infection between January 1996 and December 2004 at the two city hospitals in Sapporo and Kitami on Hokkaido Island of Japan. Geographical areas where the patients lived are indicated in Figure 1. Fourteen of the 32 patients had been included in previous studies on detection of HEV RNA and phylogenetic analysis of HEV isolates [Mizuo et al., 2002; Yazaki et al., 2003]. Serum samples collected from the 32 patients at the initial examination tested positive for anti-HEV IgG, IgM, and IgA antibodies and HEV RNA, but were negative for other viral markers of recent infection of hepatitis A virus, hepatitis B virus, hepatitis C virus, cytomegalovirus, and Epstein-Barr virus, and they were diagnosed as having hepatitis E. Informed consent was obtained from each patient in this study and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the ethics committees at Kin-ikyo Chuo hospital and Kobayashi hospital.

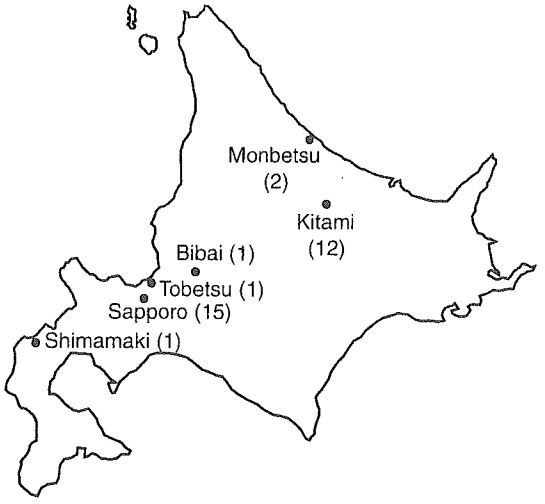


Fig. 1. Map of Hokkaido Island of Japan showing the locations of the six areas where serum samples from patients with hepatitis E were obtained. The number in the parentheses indicates the number of patients.

### Detection of Antibodies to HEV and HEV RNA

Serum samples were tested for the presence of the IgG, IgM, and IgA classes of anti-HEV antibodies by in-house enzyme-linked immunosorbent assay, using purified recombinant ORF2 protein of HEV genotype 4 that had been expressed in the pupae of silkworm, as described previously [Mizuo et al., 2002; Takahashi et al., 2005].

Serum samples were tested for HEV RNA by nested reverse transcription (RT)-polymerase chain reaction (PCR) with primers targeting the ORF2 region as described previously [Mizuo et al., 2002].

### Sequence Analysis of PCR Products

The amplification products were sequenced directly on both strands and sequence analysis was performed as described previously [Okamoto et al., 2001]. A phylogenetic tree was constructed by the neighbor-joining method [Saitou and Nei, 1987] based on the partial nucleotide sequence of the ORF2 region (412 nucleotides [nt]). Bootstrap values were determined on 1,000 resamplings of the data sets [Felsenstein, 1985].

### Statistical Analysis

Data are presented as the mean ± SD. Statistical analyses were carried out using the Welch's $t$-test for comparison of continuous variables between two groups, and the Fisher's exact probability test for comparison of proportions between two groups. Differences were considered to be statistically significant at $P < 0.05$.

## RESULTS

### Clinical and Demographic Characteristics and Laboratory Parameters

Among the 32 patients with hepatitis E, 26 (81%) were male and 22 (69%) were aged >50 years. Nine patients (28%) had an underlying disease as indicated in Table I. Five patients (Cases 22, 24, 26, 28, and 32) were seen as outpatients and did not require hospitalization, while the remaining 27 patients were hospitalized for a period of 7–110 days. The 32 hepatitis E patients had a peak alanine aminotransferase (ALT) level ranging from 152 to 5,030 IU/L and a peak aspartate aminotransferase (AST) level ranging from 59 to 5,931 IU/L (Table I); 29 patients (91%) had an elevated peak ALT and/or AST level of >1,000 IU/L. The abnormal liver function tests normalized within 2 months in 26 cases, but persisted until 64, 95, 98, or 110 days from the disease onset in the remaining 4 cases (excluding 2 cases with fulminant hepatitis E), who had severe jaundice (Cases 1, 4, and 31) or a markedly elevated ALT level (Case 2). Twenty-seven patients developed jaundice and had bilirubinemia with an increased bilirubin level ranging from 3.0 to 34.2 mg/dl, indicating that most patients contracted moderate to severe cholestasis. Seven patients were diagnosed with severe acute hepatitis in which hepatic encephalopathy did not appear during the course of the illness despite low plasma prothrombin activity (≤40%) and/or increased total bilirubin level (≥20 mg/dl); two patients with fulminant hepatitis died of hepatic failure 56 or 105 days, respectively, after the onset of the illness, in which grade II or III hepatic encephalopathy developed within 8 weeks of the onset of hepatic symptoms, with the prothrombin activity being 40% or less.

### Genetic Analysis of HEV Isolates Recovered From 32 Patients With Hepatitis E

The 412-nt sequence within ORF2 of 18 HEV isolates obtained from Cases 1, 6, 10, 13, 18, 19, 21–32 was determined. The 32 HEV isolates, consisting of these 18 HEV isolates and the 14 isolates recovered from the 14 patients in previous studies [Mizuo et al., 2002; Yazaki et al., 2003], differed from each other by up to 22.7%, and were classifiable into two groups consisting of 25- and 7 isolates. The 25 HEV isolates in one group were 87.6%–100% identical to each other, and were closely related to the prototype HEV isolate of genotype 4 (T1, accession no. AJ272108) with nucleotide identity of 85.9%–88.3%, and were only 77.6%–80.3%, 75.2%–76.9%, and 77.8%–80.0% similar to the SAR-55 isolate (M73218) of genotype 1, the MEX-14 isolate (M74506) of genotype 2, and the US1 isolate (AF060668) of genotype 3, respectively. The seven isolates in the second group were 84.0%–99.5% identical to each other and were closest to the genotype 3 HEV strains (85.7%–93.7% identity with the US1 isolate).

The phylogenetic tree constructed based on the common 412-nucleotide sequence within the ORF2 region confirmed that the 25 isolates and the remaining 7 isolates belonged to genotypes 4 and 3, respectively, and they segregated into clusters consisting of HEV strains of the same genotype that had been recovered from humans and swine in Hokkaido (Fig. 2).

### Possible Risk Factors for Acquiring Hepatitis E

None of the 32 patients had a history of travel abroad within 1 year before the disease onset, contact with pigs, wild deer or boars, nor a history of blood transfusion except for Case 18; Case 18 had been treated for aplastic anemia and received a blood transfusion just before undergoing endoscopic resection of colon cancer (44 days before the onset of hepatitis E), but the transfused blood was negative for anti-HEV IgG, IgM, and IgA as well as HEV RNA, excluding the possibility of infection via blood transfusion. Of note, 20 patients reported consumption of uncooked or undercooked pig liver 1–2 months before the onset of hepatitis E (Table I). Furthermore, 13 of the 20 patients who consumed pig liver and five other patients reported that they ingested pig intestine 1–2 months before the onset of the illness. Two patients (Cases 23 and 29) had no history of consuming pig liver/intestine, and little or no information on food consumption during the 2- to 3-month interval before the disease onset was available in five patients (Cases 1, 4, 14, 18, and 19). Excluding the five patients in whom there was little or no information on food consumption, 25 (93%) of the 27 patients were presumed to have acquired hepatitis E by the consumption of pig liver/intestine in the present study. None of the 27 patients had a history of eating meat from wild deer or boars.

### Comparison of Various Features Among the Hepatitis E Patients According to Sex, Age, and HEV Genotype

The demographic features, symptoms, physical findings, and laboratory data listed in Table II did not significantly differ between males (n = 26) and females (n = 6), between cases aged <50 years (n = 10) and those aged ≥50 years (n = 22), nor between cases aged <60 years (n = 18) and those aged ≥60 years (n = 14), except that jaundice was found significantly more frequently among males than among females (92.3% vs. 50.0%, $P = 0.0056$), and that the total bilirubin level and ALT level at the initial examination were significantly higher in males than in females ($8.3 \pm 6.7$ vs. $3.7 \pm 3.2$ mg/dl, $P = 0.0226$; $2311 \pm 1515$ vs. $1340 \pm 803$ IU/L, $P = 0.0443$, respectively). Table II compares various features among the hepatitis E patients according to HEV genotype. Of note, patients with HEV genotype 4 had significantly higher levels of total bilirubin, ALT and AST at the initial examination than patients with HEV genotype 3 ($P = 0.0022$, $P = 0.0373$, $P = 0.0453$, respectively). Further, compared with the seven patients with HEV genotype 3, the 25 patients with HEV genotype 4 had a significantly higher peak ALT level ($P = 0.0338$) and a significantly lower level of lowest prothrombin time ($P = 0.0340$).

TABLE I. Profiles of 32 Patients Who Contracted Hepatitis E Between January 1996 and December 2004 in Hokkaido, Japan

| Patient case | Age (years)/sex | Underlying disease | Year/ month of onset | Diagnosis | Peak T. Bil (mg/dl) | Peak ALT (IU/L) | Lowest PT (%) | HEV genotype | Name of HEV isolate | Consumption | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Pig liver | Pig intestine |
| 1 | 31/M | — | 1996/7 | AH | 12.6 | 1,572 | 103 | 4 | HE-JA24 | Unknown | Unknown |
| 2 | 55/M | — | 1997/12 | AH | 4.2 | 4,850 | 94 | 4 | HE-JA1[a] | No | Yes |
| 3 | 71/M | Diabetes mellitus | 1998/8 | AH | 6.2 | 4,623 | 101 | 4 | HE-JA2[a] | Yes | Yes |
| 4 | 42/M | — | 1998/10 | AHS | 24.0 | 1,744 | 22 | 4 | HE-JA3[a] | Unknown | Unknown |
| 5 | 44/M | — | 2000/1 | AH | 9.7 | 1,562 | 95 | 3 | HE-JA4[a] | Yes | Yes |
| 6 | 57/F | — | 2000/2 | AH | 1.2 | 2,341 | 76 | 3 | HE-JA25 | Yes | No |
| 7 | 72/M | Cerebral infarction | 2001/5 | AHS | 5.9 | 5,030 | 40 | 4 | HE-JA12[a] | Yes | No |
| 8 | 46/M | — | 2001/5 | AH | 6.5 | 4,100 | 68 | 4 | HE-JA13[a] | Yes | Yes |
| 9 | 57/M | — | 2001/11 | AH | 14.1 | 3,261 | 75 | 4 | HE-JA14[a] | Yes | No |
| 10 | 25/F | — | 2001/11 | AH | 1.2 | 477 | 120 | 3 | HE-JA26 | Yes | Yes |
| 11 | 51/M | — | 2002/7 | AH | 7.4 | 2,773 | 113 | 3 | HE-JA15[a] | Yes | No |
| 12 | 72/M | Rectal cancer | 2002/8 | AH | 16.3 | 1,276 | 61 | 3 | HE-JA16[a] | Yes | No |
| 13 | 72/M | — | 2002/9 | AH | 8.6 | 2,549 | 72 | 4 | HE-JA27 | Yes | No |
| 14 | 64/M | — | 2002/9 | FH | 23.1 | 1,954 | 40 | 4 | HE-JF4[a] | Unknown | Unknown |
| 15 | 61/M | Ulcerative colitis | 2002/11 | AH | 5.6 | 3,132 | 74 | 4 | HE-JA17[a] | Yes | Yes |
| 16 | 58/M | Diabetes mellitus | 2002/11 | FH | 16.3 | 2,619 | 39 | 4 | HE-JF5[a] | Yes | Yes |
| 17 | 86/M | Cerebral infarction | 2002/11 | AHS | 26.0 | 1,305 | 66 | 4 | HE-JA18[a] | Yes | Yes |
| 18 | 77/M | Aplastic anemia | 2002/12 | AH | 1.4 | 1,379 | 91 | 4 | HE-JA28 | Unknown | Unknown |
| 19 | 73/F | — | 2002/12 | AH | 6.7 | 1,966 | 105 | 4 | HE-JA29 | Unknown | Unknown |
| 20 | 56/M | — | 2002/12 | AH | 15.9 | 2,046 | 101 | 4 | HE-JA19[a] | Yes | Yes |
| 21 | 67/M | — | 2003/4 | AHS | 26.2 | 3,866 | 36 | 4 | HE-JA30 | Yes | No |
| 22 | 65/M | — | 2003/8 | AH | 9.2 | 2,291 | 80 | 4 | HE-JA31 | No | Yes |
| 23 | 61/F | — | 2003/9 | AHS | 10.6 | 4,070 | 33 | 4 | HE-JA32 | No | No |
| 24 | 52/M | — | 2003/10 | AH | 3.0 | 762 | 86 | 4 | HE-JA33 | No | Yes |
| 25 | 45/F | Rheumatoid arthritis | 2003/11 | AHS | 17.4 | 1,187 | 36 | 4 | HE-JA34 | No | Yes |
| 26 | 39/M | — | 2003/11 | AH | 0.9 | 516 | 100 | 3 | HE-JA35 | Yes | Yes |
| 27 | 75/M | — | 2003/12 | AH | 5.6 | 1,667 | 99 | 4 | HE-JA36 | Yes | Yes |
| 28 | 38/M | — | 2004/1 | AH | 3.3 | 2,916 | 100 | 4 | HE-JA37 | Yes | Yes |
| 29 | 40/M | — | 2004/7 | AH | 4.0 | 2,092 | 99 | 3 | HE-JA38 | No | No |
| 30 | 61/M | — | 2004/7 | AH | 4.3 | 4,471 | 59 | 4 | HE-JA39 | Yes | Yes |
| 31 | 52/M | Drug-induced liver injury | 2004/8 | AHS | 34.2 | 152 | 93 | 4 | HE-JA40 | Yes | Yes |
| 32 | 45/F | — | 2004/8 | AH | 0.6 | 1,230 | 100 | 4 | HE-JA41 | No | Yes |

M, male; F, female; AH, acute hepatitis; AHS, severe form of AH; FH, fulminant hepatitis; T. Bil, total bilirubin (0.2–1.2 mg/dl); ALT, alanine aminotransferase (3–36 IU/L); PT, prothrombin activity (80%–120%).

[a]These isolates have been reported previously by Mizuo et al. [2002] and Yazaki et al. [2003].


Fig. 2. Phylogenetic tree constructed by the neighbor-joining method based on the partial nucleotide sequence (412 nt; nt 5987–6398 of the HE-JA10 genome, accession no. AB089824) of the ORF2 region of 105 human and swine HEV isolates, using the prototype genotype 1 HEV isolate (SAR-55, M73218) as an outgroup. In addition to the 32 HEV isolates from the hepatitis E patients in the present study, 73 human and swine HEV isolates are included and their accession nos. are shown in parentheses. Asterisks denote swine HEV strains. The HEV strains of human and swine origin that were isolated in Hokkaido are indicated in bold type. After the slash, the name of the country other than Japan where the HEV strain was isolated is shown. Vertical bars represent clusters consisting of both human and swine HEV isolates of Hokkaido origin. Bootstrap values of >70% are indicated for the major nodes as a percentage of the data obtained from 1,000 resamplings.

TABLE II. Comparison of Various Features Between Patients With HEV Genotype 3 and Those With HEV Genotype 4

| Feature | Patients with HEV: Genotype 3 (n = 7) | Patients with HEV: Genotype 4 (n = 25) | *P*-value |
|---|---|---|---|
| Age (years) | 46.9 ± 15.0 | 59.3 ± 13.4 | NS (0.0788) |
| Male percent | 71.4 | 84.0 | NS (0.8990) |
| Symptoms [number (%)] | | | |
| Pyrexia (>38°C) | 5 (71.4) | 18 (72.0) | NS (0.7027) |
| General fatigue | 6 (85.7) | 25 (100) | NS (0.2188) |
| Nausea or vomiting | 4 (57.1) | 11 (44.0) | NS (0.4243) |
| Anorexia | 7 (100) | 20 (80.0) | NS (0.2638) |
| Abdominal pain | 0 | 6 (24.0) | NS (0.1954) |
| Pruritus | 3 (42.9) | 2 (8.0) | NS (0.0566) |
| Physical findings [number (%)] | | | |
| Jaundice | 4 (57.1) | 23 (92.0) | NS (0.0566) |
| Exanthema | 2 (28.6) | 1 (4.0) | NS (0.1129) |
| Hepatomegaly | 0 | 6 (24.0) | NS (0.1954) |
| Splenomegaly | 1 (14.3) | 1 (4.0) | NS (0.3952) |
| Laboratory data | | | |
| White blood cells (per $mm^3$) | 5024 ± 669 | 5556 ± 1792 | NS (0.2276) |
| Atypical lymphocytes (%) | 2 (28.6) | 7 (28.0) | NS (0.6572) |
| Total bilirubin (mg/dl) | | | |
| At first examination | 3.0 ± 2.6 | 8.6 ± 6.7 | 0.0022 |
| At peak | 5.8 ± 5.7 | 11.7 ± 9.1 | NS (0.0564) |
| Highest level of ≥20 mg/dl [number (%)] | 0 | 5 (20.0) | NS (0.2638) |
| Duration of elevation (days)[a] | 19.7 ± 27.5 | 35.3 ± 32.3 | NS (0.2319) |
| ALT (IU/L) | | | |
| At the initial examination | 1294 ± 954 | 2363 ± 1493 | 0.0373 |
| At peak | 1577 ± 886 | 2590 ± 1380 | 0.0338 |
| Duration of elevation (days)[a] | 35.0 ± 14.5 | 43.9 ± 22.1 | NS (0.2353) |
| AST (IU/l) | | | |
| At the initial examination | 1041 ± 817 | 1963 ± 1488 | 0.0453 |
| At peak | 1310 ± 836 | 2098 ± 1384 | NS (0.0788) |
| γ-GTP (IU/L) | | | |
| At the initial examination | 353 ± 249 | 396 ± 322 | NS (0.7177) |
| At peak | 399 ± 231 | 400 ± 324 | NS (0.9907) |
| ALP (IU/L) | | | |
| At the initial examination | 616 ± 246 | 596 ± 332 | NS (0.8590) |
| At peak | 645 ± 221 | 609 ± 323 | NS (0.7423) |
| Lowest PT percent | 94.9 ± 20.4 | 72.5 ± 27.0 | 0.0340 |
| Lowest PT percent of ≤40% [number (%)] | 0 | 7 (28.0) | NS (0.1428) |
| Admission [number (%)] | 6 (85.7) | 21 (84.0) | NS (0.7036) |
| Severe hepatitis [number (%)][b] | 0 | 9 (36.0) | NS (0.0728) |
| Fulminant hepatitis [number (%)] | 0 | 2 (8.0) | NS (0.6048) |

Total bilirubin (0.2–1.2 mg/dl); ALT, alanine aminotransferase (6–43 IU/L); AST, aspartate aminotransferase (11–40 IU/L); γ-GTP, γ-glutamyl transpeptidase (10–50 IU/L); ALP, alkaline phosphatase (80–260 IU/L); PT, prothrombin activity (80%–120%). NS, not significant.
[a]Period from the onset of illness to normalization.
[b]With peak T. Bil level of ≥20 mg/dl and/or lowest PT percent of ≤40%.

### Comparison of Various Features Among the Hepatitis E Patients According to the Severity of Hepatitis E

Table III compares various features of the patients who had the mild form of hepatitis E (n = 23) and those who had the severe form of hepatitis E (n = 9) including those with fulminant hepatitis E. Age, gender, and history of alcohol intake did not significantly differ between the two groups. Although not statistically significant, HEV genotype 4 was more prevalent among patients with the severe form of hepatitis E than among those with the mild form of hepatitis E (100% vs. 69.6%, $P = 0.0728$). Notably, the presence of an underlying disease was related to the severity of hepatitis E, being significantly more prevalent among patients with the severe form of hepatitis E than among those with the mild form of hepatitis E (55.6% vs. 17.4%, $P = 0.0454$): five of the nine patients with the severe form of hepatitis E had an underlying disease such as diabetes mellitus, cerebral infarction, rheumatoid arthritis or drug-induced liver injury. Case 31 had taken over-the-counter medicines under the suspicion of the common cold just after the appearance of the flu-like symptoms, which were probably due to hepatitis E, and 2 weeks later, he was hospitalized with the diagnoses of hepatitis E and drug-induced liver injury. In this patient, the bilirubinemia and ALT elevation persisted until 107 and 68 days, respectively, after the onset of the illness.

TABLE III. Comparison of Various Features Between Patients With the Mild Form of Hepatitis E and Those With the Severe Form of Hepatitis E

| Feature | Patients with hepatitis E | | |
|---|---|---|---|
| | Mild form (n = 23) | Severe form[a] (n = 9) | *P*-value |
| Age (years) | 54.9 ± 14.8 | 60.8 ± 13.7 | NS[b] (0.3023) |
| Male [number (%)] | 19 (82.6) | 7 (77.8) | NS (0.5544) |
| HEV genotype | | | |
| Genotype 3/genotype 4 | 7/16 | 0/9 | NS (0.0728) |
| History of alcohol intake (>80 g ethanol daily) | 7 (30.4) | 1 (11.1) | NS (0.2564) |
| Underlying disease | 4 (17.4) | 5 (55.6) | 0.0454 |

[a]With peak total bilirubin level of ≥20 mg/dl and/or lowest prothrombin activity of ≤40%.
[b]NS, not significant.

## DISCUSSION

In the present study, although little or no information about eating habits or food consumption during the last 3 months before the disease onset was available in five hepatitis E patients, among the remaining 27 patients, 25 patients reported ingestion of uncooked or undercooked pig liver and/or intestine 1–2 months before the disease onset, indicating that 93% of the 27 patients studied had a probable risk factor for acquiring hepatitis E. In previous studies, we found a high prevalence of swine anti-HEV IgG among 2- to 6-month-old Japanese pigs (58% or 1448/2500) [Takahashi et al., 2003], and identified a pair of Japanese swine and human HEV isolates of genotype 4 with 99% identity over the entire genome [Nishizawa et al., 2003]. In addition, we found that a certain proportion of packaged raw pig livers for sale in stores in Hokkaido as food (1.9% or 7/363) were contaminated with HEV, which had high nucleotide sequence identity of up to 100% with the HEV isolates recovered from Japanese patients with hepatitis E who had ingested undercooked pig liver before the disease onset and who lived in the vicinity of the stores [Yazaki et al., 2003]. Although whether pig intestines and colon for sale as food are also contaminated with HEV must be examined as well, it has been demonstrated that HEV is shed into feces, allowing transmission by the fecal-oral route, and that swine HEV replicates in the colon and intestines of infected pigs [Williams et al., 2001], suggesting that ingestion of undercooked pig intestine or colon contaminated with HEV may be another mode of transmission of HEV. In support of our speculation, our recent study indicated that HEV RNA was detectable in fecal samples obtained from the majority of nonviremic but HEV antibody-positive 4- and 5.5-month-old pigs: fecal shedding may persist longer than expected, compared with viremia in infected pigs (unpublished observations). Recently, Kato et al. [2004] reported a 69-year-old patient who died of fulminant hepatitis E in an outbreak of HEV infection in Kitami, Hokkaido of Japan: five relatives of the patient who had ingested pig liver/intestine at a barbecue restaurant, had serological markers of recent HEV infection. Therefore, zoonotic food-borne transmission of HEV via consumption of uncooked or inadequately cooked pig liver/intestine may play an important role in the occurrence of hepatitis E in Hokkaido, Japan.

Of the 32 hepatitis E patients studied, males accounted for 81% and the mean age of the 32 patients was 56.6 years. The precise reason why domestically infected hepatitis E in Japan prevails in individuals of older age and male sex remains unknown. However, Japanese people, particularly elderly males in certain geographical regions including Hokkaido [Yazaki et al., 2003], Hyogo [Tei et al., 2003], Tottori [Matsuda et al., 2003], and Nagasaki [Tamada et al., 2004], have a peculiar habit of eating raw or inadequately grilled meat and/or viscera from animals including pigs, wild deer and boars, and this may partly explain the observed phenomenon. The number of newly diagnosed cases of clinical HEV infection was highest in 2002 (ten cases), but gradually decreased in 2003 (seven cases) and in 2004 (five cases) at the two city hospitals. The yearly difference may be ascribable to changes in the level of consumption of pork and pig liver/intestine, which increased transiently in 2002 due to the marked reduction in consumption of beef after the report of the first case of bovine spongiform encephalopathy (BSE) in Japan in September 2001.

Although HEV induces a self-resolving hepatitis, hepatitis E may be fatal, especially in pregnant women in developing countries where genotype 1 HEV prevails [Purcell and Emerson, 2001]. The present study indicated that the HEV genotype and the presence of an underlying disease may influence the severity of hepatitis E. Multiple HEV strains of genotype 3 or 4 were isolated from the 32 patients with sporadic acute or fulminant hepatitis E in the present study. Of note, HEV genotype 4 tended to be associated with the severe form of hepatitis E when the genotype distribution was compared between patients with or without the severe form of acute hepatitis (including fulminant hepatitis). Although the HEV isolates were genetically heterogeneous even within the same genotype, the 25 patients with HEV genotype 4 had a significantly higher peak ALT level and a significantly lower level of lowest prothrombin activity than the seven patients with HEV genotype 3. In Japan, at least eight patients with fulminant hepatitis E have been reported thus far, including the two patients in the present study [Suzuki

et al., 2002; Ohnishi et al., 2003; Yazaki et al., 2003; Kato et al., 2004]: six of the eight patients were infected with HEV genotype 4 and, of note, five of them lived in Hokkaido. Further studies are needed to clarify whether HEV genotype is associated with the severity and outcome of acute HEV infection, similar to the advanced studies on genotypes of hepatitis B and C viruses [Okamoto et al., 1993; Feray et al., 1995; Miyakawa et al., 1995; Fung and Lok, 2004].

Age and sex were not considered as risk factors for the development of severe or fulminant hepatitis E based on the findings of the current study. Of note, the presence of an underlying disease such as diabetes mellitus, rheumatoid arthritis, or complicated liver disease was recognized as a possible risk factor for the severe form of hepatitis E. However, since a limited number of cases were evaluated in this study, a much larger study with a greater number of cases is needed to draw a definitive conclusion.

In conclusion, this study indicated that zoonotic food-borne transmission of HEV via consumption of pig liver/intestine may play an important role in the occurrence of hepatitis E in Hokkaido, where acute autochthonous hepatitis E is most prevalent in Japan. However, 2 of the 32 patients studied had never ingested pig liver/intestine nor meat from wild deer or boar and had no history of blood transfusion. Patients with transfusion-transmitted hepatitis E have been reported in Japan [Matsubayashi et al., 2004; Mitsui et al., 2004]. It remains to be determined by what other mechanisms the virus may be transmitted to humans. In view of the large number of animal species that are potentially involved, further exploration of zoonotic transmission of HEV is warranted. The HEV genotype, the presence of an underlying disease and other potential viral factors and factors related to the host deserve further investigation in much larger cohorts, in order to define the risk factors for the development of severe or fulminant hepatitis E in industrialized countries.

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特集Ⅱ 本邦におけるE型肝炎の実態

# 本邦の劇症肝炎，LOHFにおけるE型肝炎の実態*

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**Key Words** : fulminant hepatitis, late onset hepatic failure, HEV

## 劇症肝炎，LOHFの概念，成因分類とE型肝炎

劇症肝炎は「初発症状出現から8週以内にプロトロンビン時間が40%以下に低下し，昏睡Ⅱ度以上の肝性脳症を生じる肝炎」と定義され，この期間が10日以内の急性型と11日以降の亜急性型に分類される．先行する慢性肝疾患が認められる症例は劇症肝炎から除外するが，B型肝炎ウイルス(HBV)の無症候性キャリアが急性増悪した場合はこれに含めている．わが国における患者数は年間約1,000例と推定され，急性型と亜急性型がほぼ1：1でみられる[1]．比較的稀な疾患であるが，とくに亜急性型は予後不良であり，難病として扱われてきた．また，肝性脳症が出現するまでの期間が8～24週の症例は遅発性肝不全(LOHF：late onset hepatic failure)に分類している[2]．その頻度は劇症肝炎の約10分の1と少ないが，病態は亜急性型と類似して予後が不良であるため[1]，劇症肝炎の類縁疾患として扱われている．

従来，本邦の劇症肝炎，LOHFは大部分が肝炎ウイルス感染に起因すると考えられてきた．このため，平成12年までは成因をA型，B型，非A非B型および薬物性に分類し，非A非B型もウイルス性と想定してきた．また，B型はIgM-HBcが陽性例と陰性例に分類し，前者には急性感染例が，後者にはキャリア例が多く含まれるとみなしてきた．しかし，厚生労働省「難治性の肝疾患に関する研究班」が実施している全国調査(藤原研司班員)では，1998～1999年の発症例を対象にすると非A非B型の22.2%で主治医が自己免疫性肝炎を想定していることが判明した[3]．そこで，2002年に同研究班は劇症肝炎，LOHFの成因分類を抜本的に改変した(表1)[4]．

まず，非A非B型から自己免疫性を独立させ，C型をウイルス性に移すことで，残った症例を成因不明例として扱うことにした．B型は急性感染例とキャリア例に分類するが，肝炎発症時のウイルス指標を基に両者を正確に区分することは困難である[4]．そこで，急性感染例とキャリア例の確診例は，あくまでも肝炎発症前または治癒後のウイルス指標から鑑別可能な症例に限定することとした．これらが不明の症例では，IgM-HBc陽性かつHBc(200倍希釈)80%未満なら急性感染例(疑)，IgM-HBc陰性またはHBc抗体(200倍希釈)95%以上ならキャリア例(疑)とし，その他は判別不能例として扱うことにした．なお，この分類では成因不明例はウイルス性と区別して扱うが，2001年には海外渡航歴にないE型急性肝炎が報告され[5]，その中にはE型肝炎ウイルス(HEV)の国内固有株による症例が含まれ

* HEV infection in patients with fulminant hepatitis and LOHF in Japan.

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表1 劇症肝炎の成因分類(厚生労働省「難治性の肝疾患に関する研究」班：2002年)

Ⅰ．ウイルス性
　1)A型 IgM-HA抗体陽性
　2)B型 HBs抗原，IgM-HBc抗体，HBV-DNAのいずれかが陽性
　・急性感染　肝炎発症前にHBs抗原陰性が判明している症例
　・急性感染(疑) 肝炎発症前後のウイルス指標は不明であるが，IgM-HBc抗体が陽性かつHBc抗体が低力価(血清200倍希釈での測定が可能な場合は80%未満)の症例
　・キャリア　肝炎発症前からHBs抗原陽性が判明している症例
　・キャリア(疑) 肝炎発症前後のウイルス指標は不明であるが，IgM-HBc抗体陰性ないしHBc抗体が高力価(血清200倍希釈での測定が可能な場合は95%以上)のいずれかを満たす症例
　・判定不能　B型で上記のいずれをも満たさない症例
　3)C型 肝炎発症前はHCV抗体陰性で，経過中にHCV抗体ないしはHCV-RNAが陽性化した症例，肝炎発症前のHCV抗体は測定されていないが，HCVコア抗体が低力価で，HCV-RNAが陽性の症例
　4)E型 HEV-RNA陽性
　5)その他(TTV, EBVなど)
Ⅱ．自己免疫性
　1)確診 AIH基準を満たす症例またはステロイドで改善し，減量，中止後に再燃した症例
　2)疑診 抗核抗体陽性またはIgG 2,000 mg/dL以上でウイルス性，薬物性の否定された症例
Ⅲ．薬物性　臨床経過またはD-LSTより薬物が特定された症例
Ⅳ．成因不明　十分な検査が実施されているが，Ⅰ～Ⅲのいずれにも属さない症例
Ⅴ．分類不能　十分な検査が実施されていない症例

表2 劇症肝炎，LOHFにおける背景因子と予後(1998～2003年の発症例)

| | | 急性型(n=316) | 亜急性型(n=318) | LOHF(n=64) |
|---|---|---|---|---|
| 男：女(：不明) | | 167：148(：1) | 151：166(：1) | 27：37 |
| 年齢 | | 45.1±16.6[a] | 47.8±17.1** | 51.9±15.0** # |
| HBV carrier(%) | | 12.3(37/302) | 17.2(53/308)* | 4.8(3/62) ## |
| 基礎疾患[b](%) | | 32.7(102/312) | 41.5(130/313)** | 51.6(33/64)** |
| 薬物歴(%) | | 36.6(112/306) | 45.4(138/304)** | 50.0(31/62)* |
| 救命率(%) | 内科治療 | 53.7(145/270) | 24.4(57/234)** | 11.5(6/52)** # |
| | 肝移植例 | 71.7(33/46) | 81.0(68/84) | 75.0(9/12) |
| | 全体 | 56.3(178/316) | 39.3(125/318)** | 23.4(15/64)** ## |

[a]平均±SD, [b]生活習慣病，悪性腫瘍，精神疾患など，* $p<0.1$, ** $p<0.05$ vs 急性型，# $p<0.1$, ## $p<0.05$ vs 亜急性型
(文献[4]より引用)

る可能性が浮上してきた．同分類でも血清HEV-RNA陽性例をE型としてウイルス性に分類することになったが，検査の実施されている症例数はいまだ少ないのが現状である．今後，HEV-RNAの測定が普及すると，成因不明例の中からE型症例が抽出される可能性がある．

## 全国調査からみた劇症肝炎，LOHFの実態

「難治性の肝疾患に関する研究班」が実施している全国調査は日本消化器病学会，日本肝臓学会の理事，評議員の施設を対象にしており，1998～2003年に発症した劇症肝炎634例(急性型316例，亜急性型318例)，LOHF 64例が登録されている[6]．これら症例の解析から，最近はHBVキャリアおよび生活習慣病，悪性腫瘍など基礎疾患を有する症例が増加していることが判明した(表2)．HBVキャリアは急性型の12%，亜急性型の17%を占めていた．また，基礎疾患を有する症例は亜急性型とLOHFでは40%以上に達しており，その多くは薬物が投与されていた．しかし，薬物性アレルギーが成因の症例は劇症肝炎，LOHF全体の10%に過ぎず(表3)，各種薬物が劇症化に及ぼす影響に関しては今後の検討が必要である．

劇症肝炎，LOHFの成因を新分類法に準拠して解析すると(表3)，ウイルス性は急性型の71%，亜急性型の31%を占めていた．A型は大部分が急

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＜短　報＞

# タイ出張後に発症し抗体陽転が遅延し且つ分離株塩基配列がギリシャ・スペイン株に近似していた日本人E型肝炎の1例

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勝　健一[1]　高橋　和明[2]　安倍　夏生[2]　三代　俊治[2]

**緒言**：E型肝炎に関しては今猶不明点・問題点が多く残されている．最近我々は，その疫学面での不明部分と診断面での未解決問題に対して興味深い示唆を提供する，あるいは逆にE型肝炎をめぐる謎を一層深めるかもしれない，含蓄と意外性に富んだ症例を1例経験したので以下報告する．

**症例**：62歳，男性．主訴；食思不振，全身倦怠感．既往歴及び家族歴；特記事項なし．現病歴；2002年より，高血圧・高脂血症・境界型糖尿病にて当院通院中であった．2004年2月23日～3月1日までタイに出張．帰国後1週間以内に食思不振・全身倦怠感が出現し持続したため3月9日当科を受診．外来での検査にてAST 3885 U/*l*，ALT 3490 U/*l*と著明な肝障害を認めたため，即日入院となった．

**入院時身体所見**：身長169 cm，体重62 kg，意識清明，体温36.5°C，羽ばたき振戦(－)．眼球結膜に黄疸なし．腹部は軟で肝脾腫は認めず，下腿の浮腫も認めなかった．入院時血液検査；WBC 4550/$\mu l$(At-Ly 4%)，AST 3885 U/*l*，ALT 3490 U/*l*，Alb 4.1 g/d*l*，T-Bil 2.6 mg/d*l*，CRP 5.08 mg/d*l*，BUN 16 mg/d*l*，Creatinine 0.88 mg/d*l*，ChE 160 U/*l*，$NH_3$ 41 $\mu$g/d*l*，PT 52%，IgM HAV抗体陰性，IgG HAV抗体陰性，HBsAg陰性，HBsAb陽性，HbcAb弱陽性，HCV抗体陰性，HCV RNA定性試験陰性，IgG HEV抗体11(13未満)陰性，IgM HEV抗体9(30未満)陰性，HEV RNA陽性，抗核抗体陰性，抗平滑筋抗体陰性，抗ミトコンドリア抗体陰性，IgG1580 mg/d*l*，IgA160 mg/d*l*，IgM50.5 mg/d*l*，IgE194.0IU/m*l*，2'-5'OAS活性202 pMOL/d*l*．

**入院後経過**(Fig. 1参照)：入院翌日より眼球結膜に黄疸を認めT-Bil値が4.9 mg/d*l*にまで上昇(3.12)したが以後改善し，TransaminaseとPT値は入院直後から既に改善傾向が認められた．HEV RNAが陽性であったことより(抗体は陰性であったが)急性E型肝炎を最も疑い，安静と栄養管理を中心に経過観察を行った結果，速やかに肝機能検査値の改善を認め，外来通院とした．退院時(3.29)の検査では，入院時陰性であったHEV抗体がIgM 45，IgG 196と共に陽性化していた．〔HEV抗体はSRLで測定(Cosmic Corporation社製造キットを使用)〕

**HEV RNAの検出と解析**：入院直後(3.10)に採取後凍結保存されていた患者血清は，異なるプライマー設定による二つの独立したRT-PCR法[1,2]のいずれによってもHEV RNA陽性であった．一方，退院時血清(3.29採取)は，高感度PCR法[2]によってのみ陽性であった．急性期血清由来HEV RNAは，ORF 1内の326塩基(genotype III日本土着HEV株のプロトタイプであるJRA 1株のnt 124－449に

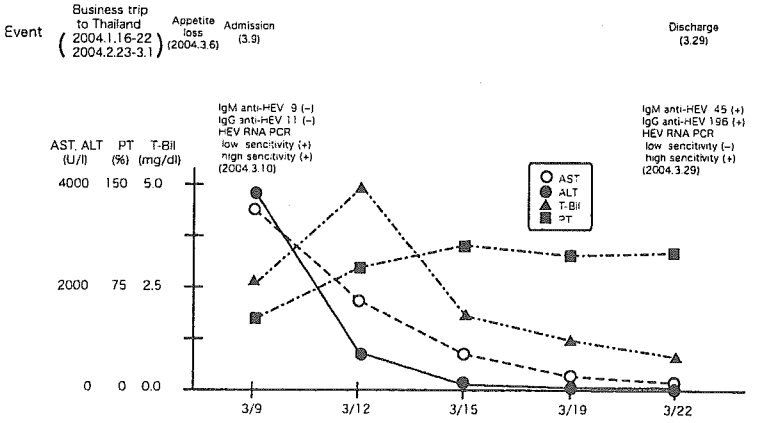


**Fig. 1**　Chronological description of the case.

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