平成23年度 肝炎等克服緊急対策研究事業『成果概要』

研究課題：経口感染する肝炎ウイルス(A型、E型)の感染防止、遺伝的多様性、および治療に関する研究
課題番号　：H21-肝炎-一般-011
予定期間　：H21年度からH23年度まで
研究代表者　：岡本宏明
所属研究機関：自治医科大学
所属部局　：医学部
職名　：教授
年次別研究費(交付決定額)：
1年目 28,105,000 円 2年目 28,105,000 円 3年目 26,419,000 円 計 82,629,000 円

Ⅰ. 研究の意義

(1) A型肝炎について、近年、低侵淫国における流行が報告され、本邦でもHAV抗体陽性者が著減している状況下、アウトブレイク発生の可能性が危惧される。また、重症、劇症化の機序が不明である。
(2) E型肝炎について、国内発生E型肝炎の過半数が感染経路不明のままであり、実態解明が急務である。一方、少なくとも約3割が動物由来感染であり、リザーバーコントロールにより感染を予防できると考えられる。臨床像の詳細な検討、治療法の確立により、重症化、劇症化、死亡の阻止が期待される。

Ⅱ. 研究の目的、期待される成果

(1) A型肝炎について、発生状況のモニタリングを実施し、重症・劇症化の機序を解明するとともに治療法を開発する。また、ワクチンの接種対象をより明確なものとし、普及・啓発を行なう。
(2) E型肝炎について、感染経路の全解明、診断・治療・予防法の確立を目標とする。その過程で、診断系が確立・普及し、E型肝炎の実態把握に繋がる。輸血血液の安全性、食の安全性の担保等が期待される。
(3) 研究代表者らによって確立されたHEVの感染培養系を駆使した研究により、HEVの増殖機構や蛋白発現様式等の解明による基礎研究の進展のみならず、診断、治療、予防など臨床領域にも資する新たな研究成果が得られることが期待される。

Ⅲ. 3年間の研究成果

・研究代表者

(1) HEV感染の全国調査(健常成人22,027人)：IgG型HEV抗体陽性率は全体で5.3%であり、男性が女性に比べて有意に高率であった(7.8% vs. 3.4%)。3人(約7,300人に1人に相当)からHEV RNAが検出された。わが国におけるHEV感染既往者は約500万人と推定された。また、年間抗体陽転率(男性0.17%、女性0.06%)から年間約12万人がHEVに新規に感染していると推定された。
(2) ヒト及びブタ、イノシシ由来のHEV（糞便、血清、肝臓)は遺伝子型の違いに因らず、PLC/PRF/5細胞とA549細胞の両者で効率よく増殖した。培養系を用い、市販ブタレバーに含まれるHEVの感染性を実証した。
(3) 岡山県で捕獲された野生イノシシからnew genotype（6型)に属するHEV株（wbJOY_06株)を発見した。
(4) HEVの放出機構:ORF3蛋白質がHEV粒子の細胞からの放出に重要な役割を果たし、放出された粒子(培養上清・血清)の表面には細胞膜成分とORF3蛋白質が存在すること、加えてORF3蛋白質がPSAPモチーフを介して小胞輸送関連因子Tsg101と結合し、細胞内膜輸送系を利用して粒子が細胞外に放出されることを明らかにした。

・研究分担者(新井雅裕)

(1) 静岡県の野生イノシシからnew genotype（5型)に属するHEV株（JBOAR135-Shiz09株)を発見した。
(2) HAVのhistorical strain（Osarizawa-1957 strain)を発掘した。
(3) 東京都内で市販されているブタレバー/大腸の約2%にHEV RNAを検出した。

・研究分担者(八橋　弘)

(1) 国立病院機構共同研究班参加 31 施設による急性肝炎の全国調査(1980 年～2010 年)を行ない、A 型肝炎が減少傾向にあること、およびE型肝炎が非 ABC 型肝炎の約 10%(2000 年以降)に相当することを確認した。

(2) パブリックコメントの機会を捉え、2009 年 8 月 14 日付で医薬食品局審査管理課の「不活化 A 型肝炎ワクチンの適応拡大に関する適応外薬の要望書」を提出した(矢野前班長、石井班友)。

・研究分担者(桶谷　真、中山伸朗)

劇症肝炎・遅発性肝不全(LOHF)の全国調査結果(1998 年～2009 年):A 型劇症肝炎の年間発症数は減少傾向にあり、2003 年以降は 10 例以下。高齢、男性、基礎疾患、合併症数が予後不良因子であった。E 型劇症肝炎は年間 1～2 例が散発的に発症しており、計 7 例の発症がみられた。高齢が予後不良因子であった。データマイニング手法による解析の結果、原因不明例が未知の肝炎ウイルス感染に起因する可能性が示唆された。

・研究分担者(鈴木一幸)

北東北地域における急性肝障害登録システムによる成因調査(2009 年 8 月～2011 年 10 月)の結果、登録された急性肝炎症例 184 例中 10 例(5.4%)が E 型であり、成因不明肝炎症例の 13.3%(10/75)を占めた。

・研究分担者(横須賀　收)

(1) Amantadine とインターフェロンαの併用療法が HAV IRES 依存性翻訳抑制、Replicon および HAV whole virus の増殖抑制に有用であった。インターフェロンλにも IRES 依存性翻訳抑制効果が認められた。

(2) 本邦の A 型肝炎重症型における IIIA 型の関与が示唆された。

(3) HAV ゲノムの複数領域の変異がウイルス複製増強及び肝炎重症化と関連する可能性が示唆された。

・研究分担者(姜　貞憲)

(1) 北海道内における HEV 感染の実態を解明:地域的 HEV 感染診断支援ネットワークである北海道 E 型肝炎研究会(道 E 研)の活動により最近 5 年間の HEV 感染症の実態が解明されつつある。

(2) 2009 年秋の札幌圏 E 型肝炎小流行及び HEV 感染集積地(札幌、北見/網走、函館)を見出し、調査した。

・研究分担者(日野　学)

北海道において 2009 年 1 月から 2011 年 10 月にかけて血清学的スクリーニング陰性かつ ALT＜61 IU/L を示す献血者 785,866 名を対象に HEV RNA スクリーニング(HEV NAT)調査を実施。HEV RNA 陽性者数は 82 名(男性 63 名、女性 19 名)「0.010%(男性 0.012%、女性 0.007%)」であった。献血前の動物内臓肉喫食率は 76%であった。

・研究分担者(李　天成)

(1) 培養 HEV 株を用い、加熱処理に対する安定性、消毒剤による不活化の条件を検討した。

(2) 培養細胞由来 HEV の不活化 E 型肝炎ワクチンとしての応用の可能性を示した。

(3) Rat HEV のウイルス様粒子(ratHEV-LPs)の作製に成功し、抗体検出系を確立するとともに、ベトナム野生ラットでの新しい遺伝子型の ratHEV の存在を明らかにした。

・研究協力者(石井孝司)

2010 年春期の A 型肝炎の流行は、主として IIIA 型の韓国大流行株(2008～2009 年)を含む 2 種類の新たな海外流入株に起因したことが判明した。

・研究協力者(中野達徳、加藤秀章、川上万里、北嶋直人)

三重県内の E 型肝炎患者 8 例及び野生イノシシ 1 頭からわが国では稀な 3 型(ヨーロッパ型)HEV を分離した。愛知県山間部で捕獲されたイノシシの 12.3%(19/154)から 4 型 HEV を検出した。岡山県内の野外捕獲ヌートリアは HEV 抗体陰性であった。兵庫県での E 型肝炎は成因不明急性肝炎例の 2.8%(3/108)であった。

Ⅳ. 今後考えられる新たな課題

(1) 全国各地の臨床例に基づく、A 型及び E 型肝炎の病態の更なる解明。

(2) 海外からの HAV 流入ルートの調査、A 型肝炎蔓延地域への渡航者へのワクチン接種の啓発。

(3) HEV の感染予防・制御に資する感染源・感染経路の更なる同定。

(4) HAV, HEV の感染実態に関する分子疫学的全把握、並びに遺伝的多様性についての理解の深化。

(5) 不活化 E 型肝炎ワクチン及び HAV、HEV に対する抗ウイルス剤の開発と応用を目指した継続的研究。

Ⅴ. 行政施策への貢献の可能性

(1) A 型肝炎について、ワクチン施策の再検討に繋がるデータが提供される。

(2) E 型肝炎について、本邦における E 型肝炎の罹患率、死亡率が減少する。

(3) 本研究の推進により、食の安全性、輸血血液の安全性が担保される。

Ⅵ. 本研究の成果（発表論文・ガイドライン・マニュアル等）

・研究代表者（二重下線）、研究協力者（一重下線）

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・研究分担者（二重下線）、研究協力者（一重下線）

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Ⅶ. Ⅲ（3 年間の研究成果）の概要図等

HAV

抗ウイルス剤の開発（横須賀班員）	Amantadine と IFNαの併用療法が HAV IRES 依存性翻訳抑制、HAV whole virus の増殖抑制に有用であり、治療への応用の可能性を示した。IFNλにも IRES 依存性翻訳抑制効果が認められた。
2010 年春期 HAV 株の解析（石井班友）	2010 年春期は例年よりも報告件数が多かったが、幸い広域アウトブレイクには進展しなかった。しかし、韓国の大流行 IIIA 株（2008 ～ 2009 年）を含め 2 種類の新たな海外流入株によることが判明したことから、引き続き慎重な監視が必要。
A 型劇症肝炎の動向（桶谷班員、中山班員）	劇症肝炎・遅発性肝不全（LOHF）の全国調査結果（1998 ～ 2009 年）：A 型劇症肝炎は減少傾向。高齢、男性、基礎疾患、合併症数が予後不良因子。IFN 投与例での救命率が有意に高い。
A 型急性肝炎の動向（八橋班員）	国立病院機構共同研究班 31 施設による急性肝炎の全国調査（1980 ～ 2010 年）：A 型肝炎が減少傾向。高齢化、重症化傾向。
尾去沢肝炎の HAV 解析（新井班員）	1957 年の「尾去沢肝炎」の患者保存血清から Osarizawa-1957 株を発掘し、全塩基配列を決定した。
ワクチン対象設定、適応拡大、普及（矢野前班長、石井班友）	本邦では 16 歳未満に対する適応がないことを受け、「不活化 A 型肝炎ワクチンの適応拡大に関する適応外薬の要望書」を提出（2009 年 8 月 14 日付）。

HEV

感染培養系を用いた研究成果（班長、李班員）	・ヒト及びブタ、イノシシ由来の HEV（糞便、血清、肝臓）が遺伝子型の違いに因らず、PLC/PRF/5 細胞と A549 細胞で効率よく増殖できることを示した。培養系において、市販ブタレバー内 HEV の感染性を実証した（班長）。 ・ORF3 蛋白質（PSAP モチーフ）が HEV の細胞からの放出に必須であり、HEV 粒子が細胞内膜輸送系を利用して出芽し、表面に細胞膜成分と ORF3 蛋白質を保有していることを明示した（班長）。 ・培養細胞由来 HEV の不活化の検討を行い、熱処理 HEV の不活化ワクチンとしての応用の可能性を示した（李班員）。
新規（5 型、6 型）HEV の同定（新井班員、班長）	野生イノシシから新規遺伝子型（5 型と 6 型）の prototype となる 2 種類の HEV 株（JBOAR135-Shiz09 株，wbJOY_06 株）を発見し、全塩基配列を決定した。
HEV 感染の全国調査（班長、日野班員）	・全国調査［30 都道県在住の約 2.2 万人（20 ～ 108 歳）］：5.3%（男性 7.8%、女性 3.4%）が IgG 型 HEV 抗体を保有。国内の HEV 感染既往者は 500 万人、年間新規感染者は 12 万人と推定（班長）。 ・全国調査［8 血液センターの約 1.3 万人（16 ～ 69 歳）］：3.4%（男性 3.9%、女性 2.9%）が IgG 型 HEV 抗体を保有（日野班員）。 ・年間抗体陽転率は男性 0.17%、女性 0.06%。東高西低（班長）。
E 型劇症肝炎の動向（桶谷班員）	劇症肝炎・LOHF の全国調査結果（1998 ～ 2009 年）：E 型劇症肝炎は年間 1 ～ 2 例が散発発生。高齢が予後不良因子。
E 型急性肝炎の動向（八橋班員）	国立病院機構共同研究班 31 施設による急性肝炎の全国調査（1980 ～ 2010 年）：E 型肝炎が非 ABC 肝炎の約 10%（2000 年以降）に相当。
北海道 E 型肝炎研究会（道 E 研）による流行監視（姜班員）	・函館地区において、北見網走株の近縁株を検出（含劇症化例）。 ・2009 年秋、札幌圏において、新札幌株による E 型肝炎小流行発生（含重症化例）。道外からの旅行者も感染（相川班友）。
北海道地域の献血者に於ける HEV-NAT の継続（日野班員）	献血者 785,866 名（2009 年 1 月～ 2011 年 10 月）における HEV RNA 陽性者は、82 名［0.010%（男性 0.012%、女性 0.007%）］。献血前の動物内臓肉喫食率は 76% であった。
北東北に於ける急性肝障害登録システムによる成因調査（鈴木班員）	2009 年 8 月から 2011 年 10 月までに登録された急性肝炎症例 184 例中 10 例（5.4%）が E 型であり、成因不明肝炎の 13.3%（10/75）を占めた。

●研究代表者の研究歴等

・過去に所属した研究機関の履歴

1983 年 5 月　自治医科大学研究生（予防生態学）
1985 年 1 月　自治医科大学助手（予防生態学）
1987 年 10 月 自治医科大学講師（予防生態学）
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1) A 型肝炎ウイルスの塩基配列の解析と遺伝子型分類
2) B 型肝炎ウイルスのサブタイプと遺伝子型に関する研究
3) B 型肝炎ウイルスの変異と病態に関する研究
4) 新規 B 型肝炎ウイルス株の同定と遺伝子解析
5) B 型肝炎ウイルスの各種測定系の開発
6) C 型肝炎ウイルスの塩基配列の解析と遺伝子型分類
7) C 型肝炎ウイルスの変異と病態に関する研究
8) C 型肝炎ウイルスの各種測定系の開発
9) デルタ肝炎ウイルスの抗体測定系の開発
10) E 型肝炎ウイルスの遺伝子配列の解析と分子疫学的研究
11) E 型肝炎ウイルスの各種測定系の開発
12) E 型肝炎ウイルスの感染培養系の確立とその応用研究
13) E 型肝炎ウイルスの増殖機構に関する研究
14) GBV-C の遺伝子解析と感染疫学に関する研究
15) TT ウイルス（アネロウイルス）の同定と分子ウイルス学的研究
16) アジア諸国（インドネシア、ネパール、タイ、ベトナム、中国、モンゴル等）に於ける肝炎ウイルス感染の実態調査と分子疫学的研究
17) 原因不明疾患に関わる未同定ウイルスの探索

・これまでの研究実績

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