health care personnel employed in the unit during their day-to-day working in the period the outbreak occurred. Consequently, it was not allowed to verify if in that period there were evident breaks in universal standard precautions during tasks and procedures performed by personnel during the care of the patients and/or in environmental control procedures; thus it was necessary to rely on healthcare workers interview and medical chart review. Both two latter sources of information could have minimized the recognition and the impact of some events able to enhance the probability of HCV transmission. On the basis of the seroconversion data and epidemiological findings, assuming there were no substantial delays in the seroconversion times, the possible chain of transmission of the infection among the hemodialysis patient harboring closely related HCV 2c should have been depicted as that reported in Figure 3. Indeed, it is well known that uremic patients receiving hemodialysis may suffer a degree of immunosuppression and may have a delayed or disturbed HCV antibody response, which results in a prolonged seronegative window phase after infection [Le Pogam et al., 1998; Savey et al., 2005]. Since serum samples obtained from the patients attending the unit at various time points were not stored and thus were no longer available for HCV RNA detection, it was impossible to determine the time in which each patient involved in the outbreak could be considered actually infected and able to transmit the infection. In other words, it was impossible to establish with certainty which patient among CT2, CT4, and CT6 was infected first and consequently when patient CT2 transmitted the infection to patient CT11. Nevertheless, routine monitoring of HCV infection as was performed in the unit, that is screening ALT monthly plus anti-HCV testing upon the admission, then every 6 months and in case of ALT increase, had permitted the detection of the outbreak. However, because of the high risk of HCV transmission in hemodialysis units even through unrecognized cases, particularly in those units where the

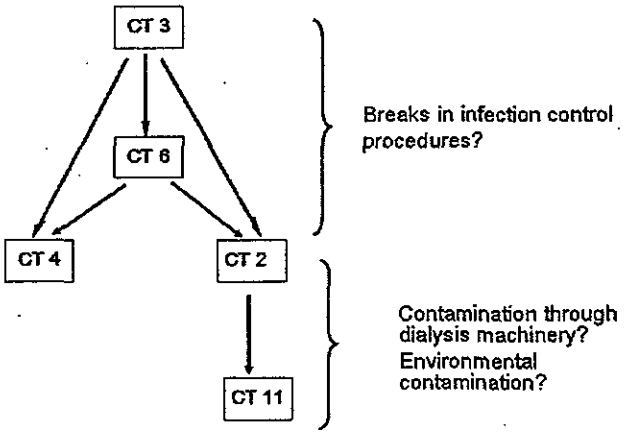

Fig. 3. Scheme of the possible chain and mechanisms of HCV transmission among genotype 2c infected patients involved in the outbreak, assuming there were no substantial delays in seroconversion times.

prevalence of HCV infected patients is high, and considering the high efficacy of an early anti-HCV therapy for newly infected patients [Gursoy et al., 2001], even this strategy may be not optimal. As suggested by other authors [Savey et al., 2005; Hmaied et al., 2006], it seems appropriate to test for HCV RNA any patient showing, at the monthly screening for ALT, a significant enzyme level increase (at least twice the baseline level of the patient) but a negative anti-HCV test and each new patient who enter the unit. To that end, it is necessary to archive monthly at least at −20°C, just for a brief time period, a serum sample for determination of HCV RNA in case of ALT elevation. However, for two of the newly infected patients (CT6 and CT11), monthly ALT screening did not help the detection of the infections, since their ALT levels had been normal until after seroconversion. Indeed, patient CT11 had dialysed outside the unit for 2 months on summer holidays (July and August 2003) and no data about his ALT levels were available for that period. On the contrary, for the two other newly infected patients (CT2 and CT4) the detection of increased ALT on monthly screening helped the diagnosis by inducing to perform and then to repeat at monthly interval (for patient CT4) the anti-HCV test. If on the occasion of the detection of an ALT levels increase in patient CT4 (May 2003) the detection of HCV RNA had been performed, the diagnosis of HCV infection probably could have been made 3–4 months early. While these facts underline uncertainty in depicting the chain of transmission in this outbreak, they also stress the importance of testing for HCV RNA whenever a significant ALT increase occurs.

After the implementation of the infection control procedures and the use of dedicated machines for anti-HCV positive patients (since January 2004), no additional cases of new HCV infection were observed in the unit. The decision of using dedicate machines for anti-HCV positive patients, that became operative from January 2004, was taken by the hospital managers according to published guidelines [Barril et al., 2004]. Isolation policy of HCV infected patients on maintenance hemodialysis by rooms, machines, and personnel, is controversial. At present, The Centers for Disease Control and Prevention does not recommend the use of dedicated machines or patient isolation [Anonymous, 2001], however in some European countries, including Italy, a good proportion of the hemodialysis units, particularly those with high prevalence of infection, currently adopt isolation strategy for HCV infected patients [EBPGEGH and ERA, 2002; Fabrizi et al., 2002; Barril and Traver, 2003; Barril et al., 2004; Di Napoli et al., 2006]. Notwithstanding the high prevalence of infection, before the outbreak occurred in the unit, no isolation measures were adopted for HCV positive patients. This was due to the lack of room for patients and to the unavailability of further hospital personnel. There are convincing arguments supporting a policy of isolation of HCV infected patients. Some prospective studies have clearly showed an important

decrease in the incidence of HCV infections by a complete isolation of the infected patients [Saxena et al., 2003]. Other studies reported a reduced number of seroconversions in unit in which all patients had a dedicated machine or some machine were dedicated for HCV infected patients [Shamshirsaz et al., 2004]. The use of dedicated machine for HCV infected patients, could be useful in units with high prevalence of HCV infection and with a low patient-personnel ratio [Barril and Traver, 2003]. On the other hand, several considerations oppose to the need to isolate HCV infected patients. HCV infectivity is lower than that of HBV. An effective isolation policy would include reliable diagnostic methods to detect HCV infected patients; this means that it would be necessary to routinely test all patients for HCV RNA. Furthermore, several investigators have been able to significantly reduce the number of seroconversion by only reinforcing infection control measures [Jadoul et al., 1998]. Finally, others authors showed the HCV transmission can occur despite the use of dedicated machine because of breaks in infection control procedures [Hmaied et al., 2006]. Even if the debate over the need for isolation policy is not resolved, there is a consensus that using dedicated machines for HCV infected patients does not exclude reinforcement of universal precautions [Delarocque-Astagneau et al., 2002; Barril and Traver, 2003].

In conclusion, molecular analysis and epidemiological investigation suggested a patient-to-patient HCV transmission in this outbreak mainly due to breaks in infection control procedures even if a related-machine transmission cannot be quite excluded in one case.

Universal infection control precautions remain the key stone in the prevention of nosocomial HCV transmission in hemodialysis units. They include avoidance of sharing equipment and devices, frequently hand washing and proper gloves use, cleaning and disinfection with virucidal agents of all the unit (instruments, machine, floor, surfaces). All these measures require continuous education, written procedures and adequate patient-personnel ratio.

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No. 41

医薬品 研究報告 調査報告書

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研究報告の概要

○サウスハンプシャーにおける急性E型肝炎国内感染率の予想外の高さ:ルーチン検査を行う時期か？
先進国特有のE型肝炎とは、流行地域への渡航歴のない者に発現したE型肝炎である。近年、英国を含む経済的に発展した多くの国に新興する疾病と認識されている。しかし、E型肝炎は現在も稀な疾患と考えられており、E型肝炎のルーチンな臨床検査は実施されていない。英国サウスハンプシャーの単一施設において2005年6月から13ヶ月の期間に診断されたE型肝炎13例について報告する。これらの患者は、ルーチンのE型肝炎血清検査を導入した新規スクリーニング手順開始後に特定された。患者は中年～高齢者で、男性の方が多かった。4名(31%)は入院を要した。RT-PCR法にて確定された症例はいずれも、英国のブタに蔓延しているHEVと相同性の高いE型肝炎ウイルス(HEV)遺伝子型3を保有した。急性肝炎発症前の2ヶ月間によく加熱しない豚肉製品を食べたり、ブタと密接な接触を持った記憶のある患者はいなかった。これに対して、同一期間中、A型肝炎の診断は2例のみ、B型肝炎の診断は4例であった。これらのデータは、原因不明の急性肝疾患を発症し、関連する渡航歴のない患者全員にルーチンのE型肝炎検査を導入することの重要性を示している。ルーチン検査は、急性肝疾患患者の臨床管理を改善しながら、E型肝炎の疫学を明らかにすることができる。

報告企業の意見	今後の対応
英国サウスハンプシャーの単一施設において2005年6月から13ヶ月の期間にE型肝炎13例が発生し、同一期間中A型肝炎は2例、B型肝炎は4例であったことから、原因不明の急性肝疾患を発症し、関連する渡航歴のない患者全員にルーチンのE型肝炎検査を実施することの重要性が示されるとの報告である。	日本赤十字社では、厚生労働科学研究「E型肝炎の感染経路・宿主域・遺伝的多様性・感染防止・診断・治療に関する研究班」と共同して、献血者におけるHEV感染の疫学調査を行っている。北海道における輸血HEV感染報告を受け、試験的に北海道では研究的NATを行うなど安全対策を実施している。また、輸血による肝炎ウイルス感染防止のため、血液中のALT値61IU/L以上の血液を輸血用から排除している。今後もHEV感染の実態に関する情報の収集及び安全対策に努める。

使用上の注意記載状況・その他参考事項等

合成血「日赤」
照射合成血「日赤」
合成血-LR「日赤」
照射合成血-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

MedDRA/J Ver.11.0J

Journal of Medical Virology 80:283–288 (2008)

Unexpectedly High Incidence of Indigenous Acute Hepatitis E Within South Hampshire: Time for Routine Testing?

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Hepatitis E indigenous to developed countries (hepatitis E^{IDC}) is a form of hepatitis E in persons with no travel history to highly endemic areas. It has been recognized recently as an emerging clinical entity in a significant number of economically developed countries including UK. However, it is still perceived as a rare disease and routine laboratory testing for hepatitis E is not performed. A series of 13 cases of hepatitis E^{IDC}, diagnosed in a 13-month period from June 2005 within a single center in South Hampshire, UK, is presented. These patients were identified after implementing a novel-screening algorithm that introduced routine hepatitis E serological investigations. Patients were middle aged or elderly and males were affected more commonly. Four patients (31%) required hospital admission. All reverse transcriptase-polymerase chain reaction (RT-PCR) confirmed cases carried hepatitis E virus (HEV) genotype-3, which bore close sequence homology to HEV circulating in UK pigs. None of these patients recalled eating undercooked pork products or close contact with pigs during the 2 months preceding the onset of acute hepatitis. In comparison, during the same period, only two cases of hepatitis A and five cases of acute hepatitis B were diagnosed. These data illustrate the importance of introducing routine hepatitis E testing in all patients with unexplained acute liver disease and absence of relevant travel history. Routine testing can clarify hepatitis E epidemiology whilst improving the clinical management of patients with acute liver disease. ***J. Med. Virol. 80:283–288, 2008.*** © 2007 Wiley-Liss, Inc.

KEY WORDS: non-travel associated hepatitis E; serology; RT-PCR

INTRODUCTION

Hepatitis E virus (HEV) is a small non-enveloped virus, with a single-stranded RNA genome of positive polarity. First documented as the cause of non-A, non-B enterically transmitted hepatitis in the eighties [Gandhi et al., 1982; Balayan et al., 1983; Bradley and Maynard, 1986], HEV was cloned and sequenced in the early nineties [Reyes et al., 1990; Tam et al., 1991] and classified as the sole member of the genus *Hepevirus*, family *Hepeviridae*, in 2004 [Emerson et al., 2004]. In developing countries, where sanitation is poor, HEV can cause epidemics of acute hepatitis E when the water supply is fecally contaminated [Tsega et al., 1991; Naik et al., 1992; Rab et al., 1997]. In this setting hepatitis E is generally a mild disease of young adults; however, pregnant women may suffer significant morbidity and mortality [Hussaini et al., 1997; Kumar et al., 2004; Boccia et al., 2006]. In developed countries, by contrast, hepatitis E is a sporadic disease identified predominantly in travelers returning from developing countries. More recently, a form of hepatitis E with no travel history to highly endemic areas has been identified and referred to as "hepatitis E indigenous to developed countries" or "hepatitis E^{IDC}" [Teo, 2006]. This form appears to affect predominantly elderly males [Sainokami et al., 2004; Ijaz et al., 2005].

Genotyping of HEV has given insights into the epidemiology of this infection. There are four main genotypes of HEV. Hepatitis E in developing countries is

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caused by genotypes 1 and 2. However, hepatitis E^{IDC} is caused by genotype 3 in most countries and by genotypes 3 and 4 in Japan [Lu et al., 2006; Okamoto, 2007]. Genotype 4 causes hepatitis E in China where it appears to be increasingly common compared to genotype 1 [Li et al., 2006]. Critically, HEV genotypes 3 and 4 are known to infect a range of animals [Wang et al., 2002; Michitaka et al., 2007], particularly pigs [Banks et al., 2004; Zheng et al., 2006; Herremans et al., 2007], suggesting that exposure to animals or animal products may be the source of infection in humans. Indeed acquisition of hepatitis E^{IDC} by dietary consumption of wild boar, deer, and pig meat or viscera, contaminated with HEV, has been documented in Japan [Tei et al., 2003; Yazaki et al., 2003; Takahashi et al., 2004; Masuda et al., 2005].

Hepatitis E^{IDC} was first reported as a clinical entity in the United Kingdom (UK) 7 years ago, following a report of four cases [McCrudden et al., 2000]. Subsequent investigations of stored serum samples, together with enhanced prospective surveillance in several UK centers, have shown that hepatitis E^{IDC} is indeed an under-diagnosed disease in UK [Ijaz et al., 2005; Lewis et al., 2006; Dalton et al., 2007]. The relatively low sensitivity [Zhang et al., 2002; Mansuy et al., 2004; Myint et al., 2006] and high costs of currently available diagnostic tests have meant that they are not used routinely in the diagnosis of unexplained abnormal liver function tests. Therefore, to date, systematic testing for hepatitis E is not routinely performed in UK diagnostic laboratories, and the true incidence and the clinical impact of this disease remain to be fully clarified.

In order to address this, a novel diagnostic algorithm, introducing routine testing for antibodies to HEV, was defined and implemented. The experience of a single diagnostic center in Hampshire, UK, is presented.

METHODS

Patients and Samples

This work was performed at Southampton University Hospital NHS Trust. Between May 2005 and June 2006, 139 (70 females, 69 males) serum samples received at the Health Protection Agency (HPA) South East Regional laboratory of Southampton, which were negative for markers of acute infection by hepatitis viruses A, B, C, Epstein–Barr virus (EBV), and cytomegalovirus (CMV), and with an ALT level greater than 300 IU/L (normal range of 10–40 IU/L), were tested for HEV IgM and IgG.

All patients with laboratory data consistent with acute hepatitis E were investigated for travel history to highly endemic areas in the 2 months preceding symptoms onset. Whenever travel history was negative, patients were asked to complete a questionnaire, which assessed contacts with animals, including pigs, dietary habits, and exposure to other jaundiced individuals. The questionnaire, developed by the Center for Infections, HPA, London (www.hpa.org.uk), after the initial cases of hepatitis E^{IDC} had been detected in UK in 1999 [Mc Crudden et al., 2000], is part of an enhanced surveillance program for this infection, in England and Wales.

HEV Serology

HEV IgM and IgG serology was performed using the Gene Lab ELISA assays, two immune enzymatic commercial tests based on recombinant antigens from HEV genotypes 1 and 2 (Genelabs Diagnostics, Singapore). Both laboratory test results were interpreted according to the directions given by the manufacturer: all samples with an optical density greater than the cut-off was considered positive. A positive HEV serology was confirmed by additionally testing a follow-up sample.

HEV Reverse Transcriptase-Polymerase Chain Reaction Assay (RT-PCR) and Genotyping

Samples reactive by the HEV IgM and/or IgG assays were additionally tested for HEV RT-PCR and genotyped, if HEV-RNA was detected, at the Center for Infections, HPA, London [Ijaz et al., 2005].

Clinical Features and Laboratory Results

Fifteen cases of acute hepatitis E were identified between May 2005 and June 2006. Two cases were diagnosed in patients of Indo-Pakistani origin who had traveled to the Indian subcontinent in the recent past. Thirteen patients were British of white European ethnicity, resident in three urban areas within a 10-mile radius of Southampton, Hampshire, UK (Fig. 1) and had not traveled to highly endemic areas in the 2 months prior to identification of raised serum ALT. Eight of the 13 patients (62%) returned the contact-tracing questionnaire. Two patients ate shellfish and three ate liver pate of unspecified animal origin in the 2 months prior to the detection of acute hepatitis. It is not known whether this consumption was occasional or habitual. During the same period no patient had consumed undercooked pork meat or had been in contact with jaundiced individuals or farm animals, including pigs. Five patients (38%) were dog owners, but no disease was reported in their pets.

Table I summarizes the patients' clinical details and laboratory results of hepatitis E^{IDC} cases. The median age was 71 years (range of 46–85 years) with 6 (46%) being 75 years of age or older; 11 (85%) were male. Twelve of the 13 initial samples were collected at the peak of the ALT value and the 13th was collected 2 weeks after the onset of jaundice, when the ALT value had normalized. HEV RNA genotype 3 was detected in 8/12 (67%) patients in the acute phase of the disease. Two HEV RNA positive patients had atypical serological profiles: one had only a detectable IgM response, without a measurable anti-HEV IgG response in spite of repeat analyses several weeks later, while the other patient had only detectable IgG.

The clinical presentations were similar in most cases. Typical features were a 2–3 weeks prodrome of malaise,