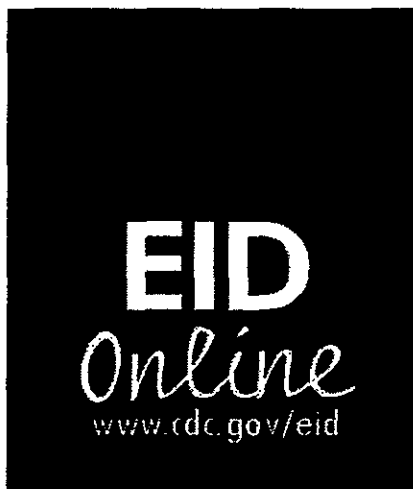


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| | | <p>性を完全には否定できないので、投与に際しては、次の点に十分注意すること。</p> <p>1) 血漿分画製剤の現在の製造工程では、ヒトパルボウイルス B19 等のウイルスを完全に不活化・除去することが困難であるため、本剤の投与によりその感染の可能性を否定できないので、投与後の経過を十分に観察すること。</p> <p>2) 現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病 (vCJD) 等が伝播したとの報告はない。しかしながら、製造工程において異常プリオンを低減し得るとの報告があるものの、理論的な vCJD 等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与すること。</p> |
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感染症の用語は、MedDRA/J version (9.0) を使用。

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H5N1 Influenza A Virus and Infected Human Plasma

To the Editor: Since January 2004, a total of 22 persons have been confirmed infected with avian influenza A virus (H5N1) in Thailand; 14 of these patients died. Three waves of outbreaks occurred during the past 2 years. The last patient of the third wave was a 5-year-old boy whose symptoms developed on November 28, 2005; he was hospitalized on December 5 and died 2 days later. The child resided in the Ongkharak District, Nakhon Nayok Province, 70 km northeast of Bangkok. Villagers informed the Department of Livestock after the patient's illness was diagnosed. Five dead chickens had been reported in this area from November 28 to December 1, 2005. Samples from these chickens could not be obtained, thus, no H5N1 testing was performed. The boy had fever, headache, and productive cough for 7 days before he was admitted to the Her Royal Highness Princess Maha Chakri Sirindhorn Medical Center. Clinical examination and chest radiograph showed evidence of lobar pneumonia. He was treated with antimicrobial drugs (midecamycin and penicillin G) and supportive care, including oxygen therapy. On December 7, the patient's condition worsened, and severe pneumonia with adult respiratory distress syndrome developed. Laboratory tests showed leukopenia ($2,300$ cells/mm³), acidosis, and low blood oxygen saturation by cutaneous pulse oximetry (81.6%). Oseltamivir was administered after his parents informed hospital staff about the boy's contact with the dead chicken. However, the boy died the same day; no autopsy was performed. On December 9, the cause of death was declared by the Ministry of Public Health to be H5N1 influenza virus.

A blood sample was collected from the patient on December 7; anticoagulation was accomplished with ethylenediaminetetraacetic acid (EDTA) for repeated biochemistry analysis and complete blood count. The plasma from the EDTA blood sample was separated 2 days later and stored at -20°C for 12 days. The sample was subsequently given to the Center of Excellence in Viral Hepatitis, Faculty of Medicine, Chulalongkorn University, for molecular diagnosis and then stored at -70°C , where specific precautions implemented for handling highly infectious disease specimens such as H5N1 influenza virus were observed. Plasma was examined by multiplex reverse transcription-polymerase chain reaction (RT-PCR) (1) and multiplex real-time RT-PCR (2), both of which showed positive results for H5N1 virus. The virus titer obtained from the plasma was 3.08×10^3 copies/mL. The plasma specimen was processed for virus isolation by embryonated egg injection, according to the standard protocol described by Harmon (3). Briefly, 100 μL 1:2 diluted plasma was injected into the allantoic cavity of a 9-day-old embryonated egg and incubated at 37°C . The infected embryo died within 48 hours, and the allantoic fluid was shown to contain 2,048 hemagglutinin (HA) units; also, subtype H5N1 was confirmed (1,2). Whole genome sequencing was performed and submitted to the GenBank database under the strain A/Thailand/NK165/05 accession no. DQ 372591-8. The phylogenetic trees of the HA and neuraminidase (NA) genes were constructed by using MEGA 3 (4) for comparison with H5N1 viruses isolated from humans, tigers, and chickens from previous outbreaks in 2004 and 2005 (Figure). The sequence analyses of the viruses showed that the HA cleavage site contained SPQRERRKKR, which differed from the 2004 H5N1 virus by an arginine-to-lysine substitution at posi-

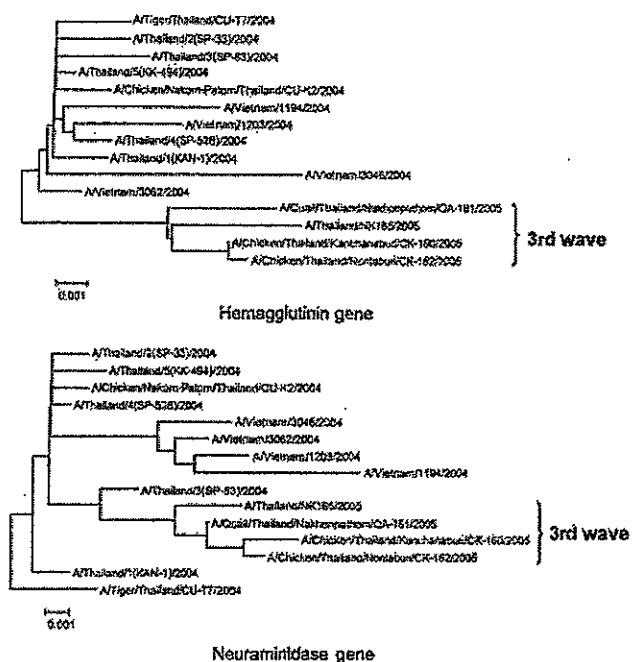


Figure. Phylogenetic analysis of the hemagglutinin and neuraminidase genes of H5N1 from study patient compared with sequences from previous outbreaks (2004–2005).

tion 341. That finding had also been observed in wild bird species during earlier outbreaks in Thailand in 2004 (5). Similar to the 2004–2005 H5N1 isolates from Thailand, a 20–amino acid deletion at the NA stalk region was observed. Moreover, the amino acid residues (E119, H274, R292, and N294) of the NA active site were conserved, which suggests that the virus was sensitive to oseltamivir. In addition, a single amino acid substitution from glutamic acid to lysine at position 627 of PB2 showed increased virus replication efficiency in mammals (6).

Observing live influenza virus in human serum or plasma is unusual. However, in 1963, low quantities of virus were isolated from blood of a patient on day 4 of illness (7), and in 1970, the virus was cultivated from blood specimens from 2 patients (8). Recently, a fatal case of avian influenza A (H5N1) in a Vietnamese child was reported. The diagnosis was determined by isolating the virus from cerebrospinal fluid, fecal, throat, and

serum specimens (9); viral RNA was found in 6 of 7 serum specimens 4–9 days after the onset of illness (10). In this case, the H5N1 virus could be isolated from plasma on day 10 after symptoms developed. This case showed the virus in the patient's blood, which raises concern about transmission among humans. Because probable H5N1 avian influenza transmission among humans has been reported (11), this case should be a reminder of the necessity to carefully handle and transport serum or plasma samples suspected to be infected with H5N1 avian influenza. Because viable virus has been detected in blood samples, handling, transportation, and testing of blood samples should be performed in a biosafety (category III) containment laboratory to prevent the spread of the virus to healthcare and laboratory workers.

We express our thanks to the Thailand Research Fund (Senior Research Scholar), Royal Golden Jubilee PhD Program and Center of Excellence in Viral

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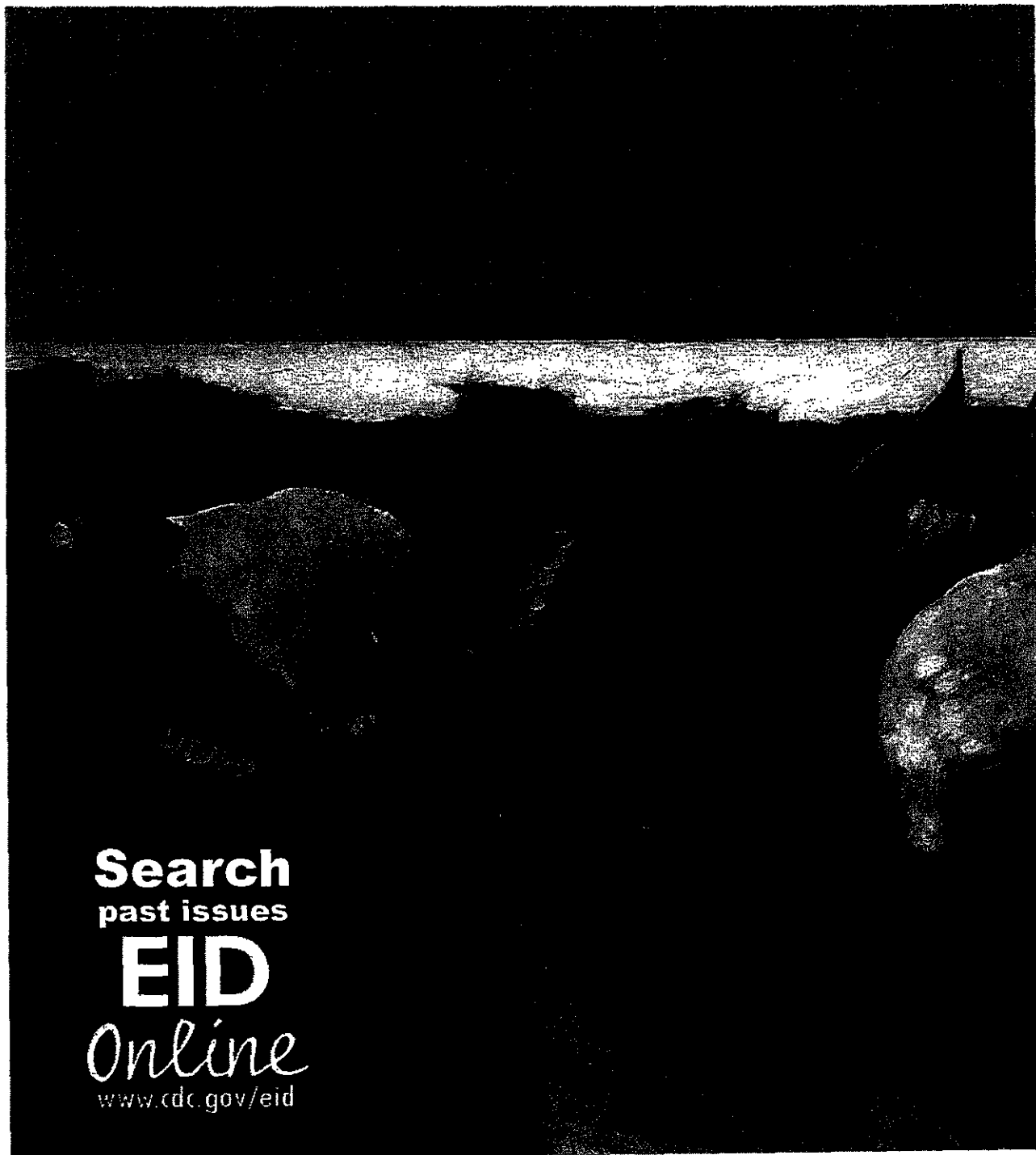
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| 研究報告の概要 | <p><目的> プリオン陽性と判定された虫垂検体から抽出された DNA のプリオン蛋白遺伝子コドン 129 の分析</p> <p><調査対象の検体> 英国の vCJD 発生調査の一つとして回顧的にプリオンについて試験を実施した 12,674 の虫垂及び扁桃の検体から陽性と判定された 3 つの虫垂検体。これら検体が得られた患者の年齢は外科手術時点で 20-29 歳であり、これら手術が行われたのは 1996-9 年である。</p> <p><結果> 3 検体の内 2 検体は十分な量の DNA が利用可能であり、両方共がプリオン蛋白遺伝子コドン 129 はバリンのホモ接合体であった。</p> <p><結論> これが、プリオン蛋白におけるコドン 129 のバリンのホモ接合体が vCJD に対する感受性が強い証拠を初めて示したものである。試験が行われた vCJD の臨床例はこれまで全て、メチオニンのホモ接合体に起こっている。そして、医原性 vCJD であることがほぼ間違いない単一例が一人の患者に見つかっているが、この患者はこの遺伝子座にメチオニン/バリンのヘテロ接合体を有していた。バリンのホモ接合体のコドン 129 プリオン蛋白遺伝子を有する vCJD 感染者は長い潜伏期間を有している可能性があり、この間に水平感染が血液ドナー又は無症候期におけるこれらの感染者に使用された汚染手術用具のいずれかから起きる可能性がある。</p> | | | | | <p>使用上の注意記載状況・ その他参考事項等</p> <p>代表としてテタノブリン-IH の記載を示す。</p> <p>2. 重要な基本的注意 (1)略 1)略 2)現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病 (vCJD) 等が伝播したとの報告はない。しかしながら、製造工程において異常プリオンを低減し得るとの報告があるものの、理論的な vCJD 等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与すること。</p> |
| | 報告企業の意見 | | | | 今後の対応 | |
| <p>プリオンについて試験を実施した12,674の虫垂及び扁桃の検体から陽性と判定された3つの虫垂検体のうち2つの虫垂検体のプリオン蛋白遺伝子コドン129がバリンのホモ体であったことから、バリンのホモ接合体のコドン129プリオン蛋白遺伝子を有するvCJD感染者は長い潜伏期間を有している可能性があり、この潜伏期間中に血液ドナー又は無症候期におけるこれらの感染者に使用された汚染手術用具のいずれかから水平感染が起きる可能性があることを示唆する報告である。</p> <p>これまで血漿分画製剤によってvCJDを含むプリオン病が伝播したとの報告はない。しかしながら、万一vCJD感染者の血漿が本剤の原料に混入した場合には、製造工程においてプリオンを低減し得るとの報告があるものの、製剤から伝播する可能性を完全には否定し得ない。そのため、弊社の血漿分画製剤の製造工程におけるTSE感染性低減に関する検証実験を加速し、自社データを早期に取得し、工程評価を行い、必要に応じて工程改善を実施する予定である。</p> | | | | <p>本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。</p> | | |



Research

Variant Creutzfeldt-Jakob disease: prion protein genotype analysis of positive appendix tissue samples from a retrospective prevalence study

James W Ironside, Matthew T Bishop, Kelly Connolly, Doha Hegazy, Suzanne Lowrie, Margaret Le Grice, Diane L Ritchie, Linda McCardle, David A Hilton

Abstract

Objective To perform prion protein gene (*PRNP*) codon 129 analysis in DNA extracted from appendix tissue samples that had tested positive for disease associated prion protein.

Design Reanalysis of positive cases identified in a retrospective anonymised unlinked prevalence study of variant Creutzfeldt-Jakob disease (vCJD) in the United Kingdom.

Study samples 3 positive appendix tissue samples out of 12 674 samples of appendix and tonsil tested for disease associated prion protein. The patients from whom these samples were obtained were aged 20-29 years at the time of surgery, which took place in 1996-9.

Setting Pathology departments in two tertiary centres in England and Scotland.

Results Adequate DNA was available for analysis in two of the three specimens, both of which were homozygous for valine at codon 129 in the *PRNP*.

Conclusions This is the first indication that the valine homozygous subgroup at codon 129 in the *PRNP* is susceptible to vCJD infection. All tested clinical cases of vCJD have so far occurred in the methionine homozygous subgroup, and a single case of probable iatrogenic vCJD infection has been identified in one patient who was a methionine/valine heterozygote at this genetic locus. People infected with vCJD with a valine homozygous codon 129 *PRNP* genotype may have a prolonged incubation period, during which horizontal spread of the infection could occur either from blood donations or from contaminated surgical instruments used on these individuals during the asymptomatic phase of the illness.

Introduction

In a prevalence study for variant Creutzfeldt-Jakob disease (vCJD), we identified three appendixes that stained positively for disease associated prion protein (PrP). We looked at 12 674 specimens (11 109 appendixes, 1565 tonsils) removed between 1995 and 2000. Most of the patients (83%) were aged 10-30 years at the time of operation.¹ This number of positive results is greater than would be predicted from the number of patients diagnosed with vCJD in United Kingdom (161 to date). Furthermore, the annual incidence of new cases of vCJD has declined from a peak in 1999. As all patients with vCJD belong to the methionine homozygous subgroup, determined by the codon 129 polymorphism in the prion protein gene (*PRNP*),² one possible explanation for this apparent discrepancy could be a differ-

ent *PRNP* genotype in the three positive cases (the prevalences of *PRNP* codon 129 genotypes in the general UK population are about 40% methionine homozygous, 10% valine homozygous, and 50% heterozygous). This possibility was supported by a slightly different pattern of immunoreactivity in the second and third positive appendix cases in comparison with clinical cases of vCJD.³ We recently identified a case of asymptomatic vCJD infection that seemed to have been transmitted by red cell transfusion in a *PRNP* codon 129 heterozygote, demonstrating that the methionine homozygous genotype is not uniquely susceptible to vCJD infection.⁴

Methods

We analysed the *PRNP* codon 129 polymorphism in the three samples of appendix tissue embedded in paraffin that stained positively for disease associated prion protein in the prevalence study. In the first case, a transmission study is currently under way using material from the remaining unstained sections. This meant that only immunostained sections were available for genotype studies and the extracted DNA was not good enough for further analysis. In the two remaining cases, as there was not sufficient material available for both transmission studies and genotype studies, and in view of possible *PRNP* influences on the staining pattern of disease associated prion protein in these cases, we used the remaining material for DNA analysis. A single 6 µm unstained paraffin section was available from each case, and these were de-paraffinised and scraped into individual microcentrifuge tubes for DNA extraction with the Puregene DNA Purification Kit (Gentra Systems, USA). Pelleted DNA was rehydrated for one hour at 65°C and then used as a template for amplification by the polymerase chain reaction (PCR), along with positive and negative control samples. PCR primers used were specific for a 506 bp region of *PRNP* containing the polymorphic sequence for the codon 129 residue. PCR products were digested at 37°C with the restriction enzyme Nsp1 (New England Biolabs, UK), which specifically recognises changes at the *PRNP* codon 129 polymorphic DNA sequence. Digest products were analysed on 1.5% agarose gels with positive controls for the codon 129 variants (MM, MV, VV).

Results

For both cases the genotype was confirmed as homozygous for the valine allele (VV) (figure). This method has been previously validated¹⁻⁵ and was controlled in our laboratory by studying the

PRNP codon 129 genotype in both paraffin embedded sections and frozen tissues from 25 other cases.

Discussion

These results give the first indication that *PRNP* codon 129 valine homozygotes may be susceptible to vCJD infection. Though the immunohistochemical technique used in our earlier study seems to be specific for disease associated prion protein,⁶ it is unlikely to be 100% sensitive, suggesting that the true prevalence of vCJD infection in the UK population may be even higher than earlier estimated (3/12 674).² Genetic studies of kuru, another orally transmitted human prion disease, found that *PRNP* codon 129 MV and VV genotypes were associated with longer incubation periods than the MM genotype.⁷ As the ethical approval for our study placed restraints on the identification of individual cases, we are not able to state with certainty the age of the patients in the positive cases at the time of surgery. We can, however, state that they were aged 20-29 years at the time of surgery, which took place in 1996-9. No clinical cases of vCJD at any age have yet been identified in *PRNP* codon 129 valine homozygotes, indicating the need for continued surveillance of all cases of vCJD in the UK.

Though it is inadvisable to overinterpret the data from only three positive cases in this study, it is perhaps surprising (given the relative prevalences of *PRNP* codon 129 genotypes in the general population) that both the positive cases analysed here were valine homozygotes. Though this may represent a chance finding, we should consider the possibility of differences in the peripheral pathogenesis of vCJD that depend on the *PRNP* codon 129 genotype. The patient who developed asymptomatic vCJD infection after red blood cell transfusion was a codon 129 heterozygote in whom both tonsil and appendix tissues were negative on staining for disease associated prion protein with methods identical to those used in this study, though the spleen and lymph nodes gave positive results.⁸ *PRNP* polymorphisms in sheep infected with scrapie also have a major influence on the incubation period and timing and distribution of disease associated prion protein in lymphoid tissues during the incubation period.⁹

A prolonged incubation period after infection with vCJD is likely to result in an asymptomatic carrier state (which cannot yet be identified), which represents a potential risk for horizontal transmission of vCJD infection by blood transfusion, blood products, or contaminated surgical instruments. These uncertainties further underline the need for continued surveillance of vCJD in the UK (including surveillance for subclinical or asymptomatic infection⁹), a requirement to continue to reduce the possibility of secondary iatrogenic transmission, and the inclusion of carrier states and susceptibility to vCJD infection in all *PRNP* codon 129 genotypes in future disease modelling.

Contributors: JWI and DAH were responsible for the prevalence study and the analysis of the results, including the selection of the cases for analysis, and drafted and modified the manuscript. MTB established the methods for DNA extraction and analysis, designed and executed the validation study, and drafted and modified the manuscript. KC and DH performed the DNA extraction on the test materials and in the validation study, and modified the manuscript. MLeC, SL, DLR, and LMcC identified cases for the validation study and prepared the paraffin sections for DNA analysis and modified the manuscript. JWI is guarantor.

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Competing interest: None declared.

Ethical approval: The prevalence study received approval from the South and West multi-centre research ethics committee (MREC reference 99/6/32) and for each of the centres included, appropriate local research ethics committee approval.

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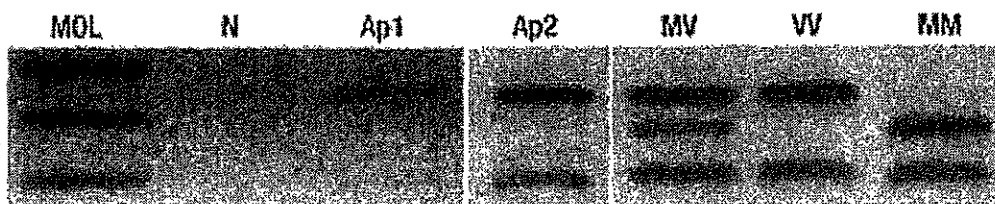
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Restriction digest pattern for *PRNP* codon 129 genotype analysis in two paraffin section tissue samples (shown combined). The test sample results clearly show banding patterns equivalent to the VV genotype control (Mol=molecular weight ladder, N=PCR negative control, Ap1=appendix tissue from positive case 2, Ap2=appendix tissue from positive case 3, positive control samples from *PRNP* codon 129 MM, MV, and VV genotypes)

What is already known on this topic

A recent prevalence study of accumulation of prion protein (as a marker for variant Creutzfeldt-Jakob disease) in appendix and tonsil specimens in the UK, found three cases in 12 674 samples, which is more than expected from the current number of clinical cases of vCJD

What this study adds

Analysis of DNA from two of the three positive samples found they were valine homozygotes at codon 129 in the prion protein gene, indicating that this genetic subgroup (which is a different subgroup to that in which all cases of vCJD so far have occurred) is susceptible to vCJD infection

Individuals with this genotype may have a prolonged incubation period with subclinical infection and could cause secondary spread of vCJD by blood transfusion or surgery

医薬品 研究報告 調査報告書

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| <p>識別番号・報告回数</p> | | | <p>報告日</p> | <p>第一報入手日 2006. 3. 25</p> | <p>新医薬品等の区分 該当なし</p> | <p>機構処理欄</p> |
| <p>一般的名称</p> | <p>解凍人赤血球濃厚液</p> | | | <p>Yamada M; Variant CJD Working Group, Creutzfeldt-Jakob Disease Surveillance Committee, Japan. Lancet. 2006 Mar 11;367(9513):874.</p> | <p>公表国 日本</p> | |
| <p>販売名(企業名)</p> | <p>解凍赤血球濃厚液「日赤」(日本赤十字社) 照射解凍赤血球濃厚液「日赤」(日本赤十字社)</p> | | <p>研究報告の公表状況</p> | | | <p>使用上の注意記載状況・その他参考事項等</p> |
| <p>研究報告の概要</p> | <p>○変異型クロイツフェルト・ヤコブ病(vCJD)日本初の症例は周期性脳波を示していた 2004年2月、50歳の日本人男性の症例がCJDサーベイランス委員会に報告された。患者は1990年代前半に英国に24日間、フランスに3日間、vCJDの報告がない欧州の他の国に2週間滞在していた。手術歴や輸血歴はなく、プリオン病の家族歴もなかった。2001年6月、48歳の時に漢字を書くことが困難になった。2001年10月、興奮性、人格変化、記憶障害など精神症状を発現。後に異常感覚、運動失調、認知症、異常行動が見られた。2002年8月のMRIでは、視床部にわずかに高信号が認められた。2003年1月、認知症、運動失調、過反射を示した。MRI画像は、視床部に対称性の高信号域を認めた。脳波画像(EEG)は徐波化を示したが、孤発性クロイツフェルト・ヤコブ病(sCJD)に特徴的な周期性同期性放電(PSD)は認められなかった。脳脊髄液の14-3-3蛋白質は陽性だった。コドン129(メチオニン/メチオニン)と219(グルタミン酸/グルタミン酸)に変異はなかった。この時点ではvCJD可能性例の診断基準を満たしていた。運動機能と認知機能は急速に低下した。 2003年12月、無動性無言、ミオクローヌス、錐体路徴候を示した。MRI像は、尾状核、被殻、視床、大脳皮質に高信号を認めた。信号強度は視床より尾状核と被殻の方が高かった。EEGはPSDを示しsCJDの可能性例と診断された。2004年12月、患者は肺炎で死亡した。剖検結果はvCJDの特徴を示した。前頭葉に花弁状空胞が見られ、プロテアーゼ抵抗性PrP^{Sc}は、Collingeの4型PrP^{Sc}、すなわちParchiの2B型だった。 これは日本初のvCJD確定例である。進行性の神経精神疾患はvCJDを示したが、罹病期間は通常(中央値14カ月)よりはるかに長かった。これまで、vCJDで視床枕徴候が陽性から陰性になった症例は複数報告があったが、PSDを伴うvCJD症例は初めてである。この症例は、PSDによってvCJDの可能性が除外されないことを示しており、生前診断でvCJDを見逃さないため、WHOのvCJDの定義の修正を提案する。今回の患者がどこで病原体に暴露したのかは明らかではない。患者の渡英時、英国でのBSE流行は続いており、このとき暴露の可能性がある食品を食べたことは確認されているが、フランスや他の国、または日本で感染した可能性も否定できない。英国で感染したと仮定すると、暴露から発症までの潜伏期間は11.5年となる。</p> | | | | | <p>解凍赤血球濃厚液「日赤」 照射解凍赤血球濃厚液「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</p> |
| <p>報告企業の意見</p> | | | <p>今後の対応</p> | | | |
| <p>変異型クロイツフェルト・ヤコブ病(vCJD)日本初の症例は周期性脳波を示し、sCJDの可能性例と診断されたが、剖検結果はvCJDの特徴を示していたとの報告である。</p> | | | <p>今後も引き続き、プリオン病に関する新たな知見及び情報の収集に努める。</p> | | | |