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Subject PRO/AH/EDR> CJD (new var.) update 2007

CJD (NEW VARIANT) UPDATE 2007
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A ProMED-mail post
<http://www.promedmail.org>
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International Society for Infectious Diseases
<http://www.isid.org>

[The definition of the designations deaths, definite cases, probable vCJD cases, and the case definitions can be found by accessing the Department of Health website, or by reference to a previous ProMED-mail post in this thread (for example, CJD (new var.) - UK: update March 2002 20020305.3693).

Data on vCJD cases from other parts of the world are now included in these updates whenever available.

Also, data on other forms of CJD (sporadic, iatrogenic, familial and GSS) are now included when they have some relevance to the incidence and etiology of vCJD. - Mod.CP]

In this update:
[1] UK: Department of Health monthly vCJD and CJD statistics, Mon 8 Jan 2007
[2] EUROCJD data as of 8 Jan 2007
[3] National (US) Prion Disease Pathology Surveillance Center Data: 31 Dec 200
[4] Prion reduction by blood filtration
[5] Blood transfusion risk in France
[6] Blood transfusion risk in UK

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[1] UK: Department of Health monthly vCJD and CJD statistics, Mon 8 Jan 2007
Date: Mon 8 Jan 2007
From: ProMED-mail <promed@promedmail.org>
Source: UK Department of Health, Monthly Creutzfeldt-Jakob Disease Statistics [edited]
<http://www.gnn.gov.uk/environment/fullDetail.asp?ReleaseID=254733&NewsAreaID=

The Department of Health is today [Mon 8 Jan 2007] issuing the latest information about the numbers of known cases of Creutzfeldt-Jakob disease. This includes cases of variant Creutzfeldt-Jakob disease [abbreviated in ProMED-mail as CJD (new var.) or vCJD], the form of the disease thought to be linked to BSE (bovine spongiform encephalopathy).

Definite and probable CJD cases in the UK, as of Fri 5 Jan 2007

Summary of vCJD cases - deaths

Deaths from definite vCJD (confirmed): 112
Deaths from probable vCJD (without neuropathological confirmation): 46
Deaths from probable vCJD (neuropathological confirmation pending): 0
Number of deaths from definite or probable vCJD (as above): 158

Summary of vCJD cases - alive

Number of probable vCJD cases still alive: 7

Total

Number of definite or probable vCJD (dead and alive): 165

(The next table will be published on Mon 5 Feb 2007).

Since the previous monthly statistics were released on Mon 4 Dec 2006, the total number of deaths from definite vCJD remains unchanged and stands at 158. The overall total number of definite or probable vCJD cases (dead and alive) has increased by one (surviving) individual and becomes 165.

These data are consistent with the view that the vCJD outbreak in the UK is in decline. The peak number of deaths was 28 in the year 2000, followed by 20 in 2001, 17 in 2002, 18 in 2003, 9 in 2004, 5 in 2005, and 5 in 2006.

Totals for all types of CJD cases in the UK in 2006

As of Fri 5 Jan 2007, in the UK in the year 2006, there were 106 referrals, 53 deaths from sporadic CJD, 5 from familial CJD, 5 from variant CJD, 3 from GSS and one from iatrogenic CJD.

During the period from 1995, when vCJD was 1st diagnosed, up to the present, there have been 953 deaths from all forms of CJD including the 158 deaths attributable to definite or probable vCJD.

[These data are accessible via
<http://www.gnn.gov.uk/environment/fullDetail.asp?ReleaseID=254733&NewsAreaID=

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ProMED-mail
<promed@promedmail.org>

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[2] EUROCJD data as of 8 Jan 2007
Date: Sun 31 Dec 2006
From: ProMED-mail <promed@promedmail.org>
Source: EUROCJD [edited]
<http://www.eurocjd.ed.ac.uk/vcjdworldeuro.htm>

The European And Allied Countries Collaborative Study Group of CJD (EUCJD)

This website includes information from 2 projects funded by the European Commission. The EUROCJD project started in 1993 and compares data from national registries in Australia, Austria, Canada, France, Germany, Italy, the Netherlands, Slovakia, Spain, Switzerland and the UK. The NEUROCJD project started in 1998 after the European Union Council recommended that epidemiological surveillance of CJD should be extended to all member states. The member states involved in this project are Belgium, Denmark, Finland, Greece, Iceland, Ireland, Israel, Norway and Portugal. Both projects are coordinated from the U.K. National CJD Surveillance Unit based in Edinburgh.

Current data as at December 2006*

Country / Total No. of Primary cases (No. alive) / Cumulative residence in UK (>6 months) / Secondary transmission by blood transfusion

United Kingdom / 163 (7) / 165 / 2 (0)
France / 21 (2) / 1 / 0
Republic of Ireland / 4 (1) / 2 / 0
Italy / 1 (0) / 0 / 0
USA / 3 (1*) / 2 / 0 / 0

Canada / 1 (0) / 1 / 0
Saudi Arabia / 1 (1) / 0 / 0
Japan / 1** (0) / 0 / 0
Netherlands / 2 (0) / 0 / 0
Portugal / 1 (1) / 0 / 0
Spain / 1 (0) / 0 / 0

Total / 198 (12) / - / 2

Footnotes
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* The 3rd US patient with vCJD was born and raised in Saudi Arabia and has lived permanently in the United States since 2005. According to the US case report, the patient was most likely infected as a child when living in Saudi Arabia.
** The case from Japan had resided in the UK for 24 days in the period 1980-1996.

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[3] National (US) Prion Disease Pathology Surveillance Center Data: 31 Dec 200
Date: Mon 8 Nov 2006
From: ProMED-mail <promed@promedmail.org>
Source: CJD Surveillance, National Prion Disease Pathology Surveillance Center [edited]
<http://www.cjdsurveillance.com/resources-casereport.html>

[The Prion Disease Surveillance Data remains essentially unchanged. Previously, the Moderator noted an apparent inconsistency between the national data and a figure circulated by the Virginia Department of Health. The Virginia Department of Health/CDC report cited above lists 3 cases -- 2 cases probably contracted in the U.K. -- and the young adult described above who was born and raised in Saudi Arabia. The EUROCJD data for October 2006 in part (2) above also lists 2 U.S. cases, both assumed to have been contracted in the U.K. The U.S. National Prion Disease Pathology Surveillance Center Data published on 8 Nov 2006, on the other hand, lists only a single U.S. case believed to have been contracted in the U.K. The following clarification has been provided by Ermias Belay of the CDC/CCID/NCZVED]:

The inconsistency noted by Mod.CP is appropriate, but it stems from the fact that the EUROCJD data is for October 2006 and was not updated to include the 3rd U.S. vCJD case in a Saudi man announced by CDC in November 2006. The data from the U.S. National Prion Disease Pathology Surveillance Center lists only cases confirmed by the center. The only U.S. vCJD case tested at the pathology center is the 1st U.S. case. The 2nd case was tested and confirmed in England and the 3rd case was tested and confirmed by UCSF. Incidentally, the 1st Saudi vCJD case was tested and confirmed by the U.S. pathology center, but the patient was never in the United States (hence not attributed to the U.S.); brain biopsy tissue was shipped to the U.S. by Saudi physicians.

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[ProMED-mail thanks Ermias Belay for clarifying the situation. - Mod.CP]

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[4] Prion reduction by blood filtration

Date: Fri 22 Dec 2006
From: ProMED-mail <promed@promedmail.org>
Source: BBC News online [edited]
<http://news.bbc.co.uk/1/hi/health/6200107.stm>

Scientists hail blood filtration technique

Scientists have found a way to remove disease-causing proteins from infected animal blood, which they hope may fight the human form of mad cow disease. UK and US researchers identified a molecule which removed the prion proteins from blood infected with scrapie, the Lancet reports. Scrapie, which can affect sheep, is related to variant CJD. It is hoped the technique could also treat human blood. But a blood transfusion expert said it 1st had to be properly assessed. Prion diseases, including bovine spongiform encephalopathy (BSE) -- or mad cow disease -- and variant Creutzfeldt-Jakob Disease (vCJD), are fatal neurodegenerative diseases that occur after years of incubation with no apparent symptoms.

In the UK, 3 people have died from vCJD after receiving blood from donors who later went on to develop the disease. Globally, there have been 200 cases of vCJD reported, 164 of which were in the UK. The researchers, including scientists from Cambridge University, suggest removing the infectious ability of prions -- mis-formed proteins -- might be one of the best ways of reducing the risk of vCJD transmission through blood. They screened millions of molecules and found that one, called L13, binds prion protein (PrP), removing it from the blood.

The team checked this by passing 500 ml of scrapie-infected hamster blood through a filter that removes white blood cells, something which is done to all blood donated from transfusion in the UK. When they injected the blood into 99 hamsters, 15 became infected with scrapie. But when they passed treated blood through devices containing the removal molecule and injected 96 hamsters with it, they found that none became infected. L13 was also found to bind to PrP from human infections of vCJD, suggesting that it may also remove prion infectivity from human blood. Dr. Robert Rohwer, from the Veterans Affairs Medical Center, at the University of Maryland, Baltimore, who was involved in the study, said: "Removal of vCJD infectivity by adsorption gets around the extremely difficult problem of detecting the very low concentrations of these agents in blood, especially during the long asymptomatic period when people donate.

Writing in the Lancet, Marc Turner of the Edinburgh Blood Transfusion Centre, said there were concerns about how best to check whether the technology worked, as there is nothing to compare it against. There are also worries that passing blood through filters may cause blood to be caught up in the device and therefore lost, or could alter the blood's properties. He added that: "The UK and Irish Blood Services have produced quality, efficacy and operational specifications for such filters and are considering an assessment program that will include independent investigation of efficacy and clinical safety studies. Until these technologies can be clinically and operationally assessed, the best protection against the uncertain risk of transfusion-associated prion disease remains in

ensuring that blood products are used only if needed and that the uncertainties surrounding potential risks are communicated effectively to patients and to the public at large."

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[The Lancet paper which is the subject of this report is entitled: "Reduction in infectivity of endogenous transmissible spongiform encephalopathies present in blood by adsorption to selective affinity resins," authored by Luisa Gregor and 8 others, <http://www.thelancet.com/journals/lancet/article/PIIS0140673606698978/abstrac

The Summary reads as follow:
"Background: Transmissible spongiform encephalopathies (TSE) can be contracted through blood transfusion. Selective adsorption of the causative agent from donated blood might be one of the best ways of managing this risk. In our study, affinity resin L13, which reduces brain-derived infectivity spiked into human red blood cell concentrate by around 4 log10ID50, and its equivalent, L13A, produced on a manufacturing scale, were assessed for their ability to remove TSE infectivity endogenously present in blood.

Methods: 500 ml of scrapie-infected hamster whole blood was leucoreduced at full scale before passage through the affinity resins. Infectivity of whole blood, leucoreduced whole blood (challenge), and the recovered blood from each flow-through was measured by limiting dilution titration.

Findings: Leucoreduction removed 72 percent of input infectivity. 15 of 99 animals were infected by the challenge, whereas none of the 96 or 100 animals inoculated with the final flow-throughs from either resin developed the disease after 540 days. The limit of detection of the bioassay was 0□2 infectious doses per ml. The overall reduction of the challenge infectivity was more than 1.22 log10ID. The results showed removal of endogenous TSE infectivity from leucoreduced whole blood by affinity ligands. The same resins adsorb normal and abnormal prion protein from human infections with variant, sporadic, and familial Creutzfeldt-Jakob disease, in the presence of blood components.

Interpretation: TSE affinity ligands, when incorporated into appropriate devices, can be used to mitigate the risks from TSE-infected blood, blood products, and other materials exposed to TSE infectivity." - Mod.CP]

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[5] Blood transfusion risk in France
Date: Tue 26 Dec 2006
From: Terry Singeltary <flounder9@verizon.net>
Source: Transfusion Clinique et Biologique, .11.003, 2006 [edited]
<http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6VN7-4MMP63G-2&_use

Transfusion risk analysis with regard to vCJD in France

(By M. Martin, J.-F. Legrasa, E. Pouchola and J.-H. Trouvina (DEMEB, departement de l'evaluation des produits biologiques, 143-147, boulevard A.-France, 93285 Saint-Denis cedex, France)

ABSTRACT: The latest updates (February 2004 and February 2005) of the analysis of the risk of transmission of the agent of Creutzfeldt-Jakob disease (CJD) by blood and blood products in France 1st reported in 2000, were triggered by the 2 cases of probable transmission of variant CJD (vCJD) by transfusion reported in the UK and the notification of 2 French cases of vCJD who had been blood donors on several occasions before clinical onset. Even though some figures of the quantitative assumption used in the risk analysis have been modified since 2000, the conclusion as regards the risk for blood cellular component is considered unchanged: it can be assumed that one unit of labile blood products will contain more than one infectious unit if the donor is incubating the disease. Therefore, the residual risk of receiving by transfusion one infectious blood unit is dependent on the prevalence of subjects incubating the disease in the blood donor population. For this particular aspect, the expected number of clinical vCJD cases to occur in France has been lowered since 2000. However, the worst-case scenario of 300 cases in the next 60 years has been maintained in the risk analysis, leading to the hypothesis that one blood donor per 120 000 could be infectious. In conclusion, the risk of getting one infectious blood unit is considered probable to a level of 1/120 000, but the benefit outweighs the risk if the use of transfusion is restricted to well justified indications and if patients are informed a priori and a posteriori.

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[6] Blood transfusion risk in UK
Date: Tue 26 Dec 2006
From: Terry Singeltary <flounder9@verizon.net>
Source: Transfusion Clinique et Biologique,.11.007, 2006 [edited]
<http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6VN7-4MMP63G-5&_use

vCJD and blood transfusion: risk assessment in the United Kingdom
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(By S.A. Dobra, a, and P.G. Bennettam Department of Health, Wellington House, 133-155 Waterloo Rood, London SE1 8UG, UK)

ABSTRACT: The risk of vCJD transmission via blood transfusion depends on potential levels of infectivity, recipients' exposure to infected donors and individual susceptibility. On infectivity, SEAC (the UK's main scientific advisory committee on TSEs), has published an updated position statement. Based on animal models, this suggests that infectivity is split roughly equally between leucocytes and plasma, with negligible levels directly associated with red cells or platelets. Risk assessments are now therefore based on the amounts of plasma and leucocytes within each component as transfused. Recipients' exposure to infection depends critically on the prevalence of infection in the population. This remains unknown, so a range of assumptions must still be considered. A further consideration is the likelihood of any infected donors' blood being infective. Those infected in the primary outbreak will now have been incubating vCJD for 10-25 years. Current thinking is that blood may be more infective later in the incubation period. This reinforces the case for a precautionary approach to transmission risks,

despite the small number of incidents seen so
far. Exposure will also depend on how many donors
contributed components to a given individual.
Recent work has shown that more patients receive
large numbers of units than previously thought.
These highly-transfused patients are a particular
cause for concern. The current precautionary
assumption is of all recipients being susceptible
to infection by transfusion, though incubation periods may differ markedly.

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[see also:
CJD (new var.), blood transfusion risk 20061208.3468
CJD, transmission risk - Canada (ON) 20061207.3457
CJD (new var.) update 2006 (12) 20061205.3431
CJD (new var.) update 2006 (11) 20061106.3190
CJD (new var.) update 2006 (10) 20061002.2820
CJD (new var.) update 2006 (09) 20060904.2519
CJD (new var.) update 2006 (08) 20060807.2207
CJD (new var.) update 2006 (07) 20060703.1831
CJD (new var.) - Netherlands: 2nd case 20060623.1741
CJD (new var.) update 2006 (06) 20060605.1566
CJD (new var.) update 2006 (05) 20060508.1332
CJD (new var.) update 2006 (04) 20060404.1005
CJD (new var.) update 2006 (03) 20060306.0728
CJD (new var.) - UK: 3rd transfusion-related case 20060209.0432
CJD (new var.) update 2006 (02) 20060206.0386
CJD (new var.) update 2006 (01) 20060111.0101
CJD (new var.) update 2006 20060111.0101
2005

CJD (new var.) update 2005 (12) 20051209.3547
CJD (new var.) update 2005 (11) 20051108.3270
CJD (new var.) update 2005 (10) 20051006.2916
CJD (new var.) update 2005 (09) 20050905.2627
CJD (new var.) update 2005 (08) 20050801.2237
CJD (new var.) update 2005 (07) 20050703.1889
CJD (new var.) update 2005 (06) 20050607.1584
CJD (new var.) update 2005 (05) 20050505.1243
CJD (new var.) update 2005 (04) 20050405.0982
CJD (new var.) update 2005 (03) 20050308.0687
CJD (new var.) update 2005 (02) 20050211.0467
CJD (new var.) - UK: update 2005 (01) 20050111.0095
2004

CJD, genetic susceptibility 20041112.3064
CJD (new var.) - UK: update 2004 (14) 20041206.3242
CJD (new var.) - UK: update 2004 (13) 20041103.2977
CJD (new var.) - UK: update 2004 (12) 20041023.2871
CJD (new var.) - UK: update 2004 (11) 20041008.2758
CJD (new var.) - UK: update 2004 (10) 20040909.2518
CJD (new var.) - UK: update 2004 (09) 20040809.2199
CJD (new var.) - UK: update 2004 (08) 20040806.2150
CJD (new var.) - UK: update 2004 (07) 20040706.1807
CJD (new var.) - UK: update 2004 (06) 20040608.1535
CJD (new var.) - UK: update 2004 (05) 20040510.1262
CJD (new var.) - UK: update 2004 (04) 20040406.0937
CJD (new var.) - UK: update 2004 (03) 20040314.0713
CJD (new var.) - UK: update 2004 (02) 20040202.0400
CJD (new var.) - UK: update 2004 (01) 20040106.0064
CJD (new var.) - France: 8th case 20041022.2864
CJD (new var.) - France: 9th case 20041123.3138
CJD (new var.), blood supply - UK 20040318.0758
CJD (new var.), carrier frequency study - UK 20040521.1365
2003

CJD (new var.) - UK: update 2003 (13) 20031216.3072
CJD (new var.) - UK: update 2003 (01) 20030108.0057
2002

CJD (new var.) - UK: update Dec 2002 20021207.5997
CJD (new var.) - UK: update Jan 2002 20020111.3223

医薬品
医薬部外品　研究報告　調査報告書
化粧品

識別番号・報告回数		回	報告日 年　月　日	第一報入手日 2006 年 12 月 8 日	新医薬品等の区分 該当なし	総合機構処理欄
一般的名称			研究報告の公表状況	Atypical transmissible spongiform encephlopathies (TSEs) in ruminants Baron, T. et al., Vaccine, in press, available on line at www.sciencedirect.com on 13 Nov. 2006	公表国 フランス	
販売名 (企業名)						

研究報告の概要

この報告文献は反芻動物における感染性海綿状脳症 (TSE) －特にヒツジにおける異型 TSE－に焦点をおいた現在の知見の概要である。宿主異常タンパク質であるプリオンタンパク (PrP^{res}／正常プリオンタンパクと異なりプロテアーゼ消化耐性をもつ) の感染組織への蓄積は TSE の重要な特徴である。ウエスタン・ブロット法と免疫組織化学的分析により，ウシ海綿状脳症 (BSE) 感染動物の脳から分離した PrP^{res} とスクレイピー感染したヒツジから分離した PrP^{res} の識別は可能である。これらの技術により，フランスでは，BSE が確認された PrP^{res} と類似した分子構造を持つヤギ TSE 自然発生症例を識別出来た。マウスにおける感染実験では，ヤギから分離した感染因子と BSE 病原体の区別は不可能であった。また，ヒツジにおける TSE 自然発生症例のその他の分離株では，ウエスタン・ブロット法で検出された特徴と実験的に誘発された BSE 症例での PrP^{res} の特徴が非常に類似していることが確認された。ヒツジ PrP を過剰発現させたトランスジェニックマウスでの予備感染実験の結果では，異なった TSE 病原体「株」の存在が示唆された。ヨーロッパ諸国の中では，長年，小型反芻動物からの異型 TSE 分離株の存在が知られている。これらの症例では，病原性プリオンタンパクは脳内部での特異的な分布に加えて，プロテアーゼ感受性の変化や新規の電気泳動パターンを示していた。そのうえ，この内の数例は，従来のスクレイピー又は BSE に耐性のあるプリオン遺伝子型をもつヒツジで発現していた。これらの TSE はヒツジ PrP 過剰発現マウスに感染することが確認された。また，ヨーロッパでは畜牛でも異型 TSE が発生している。これらの症例では，従来の BSE によって発症したものと比較すると，PrP^{res} の糖鎖付加パターンが変化していた。ウシとマウス両方のモデルでは，アミロイド斑として知られている新型の病変と同様に海綿状脳障害独特の分布とも関連していた。反芻動物におけるこのような異型 TSE の起源はまだ不明あるが，ヒトにおけるクロイツフェルト・ヤコブ病の「散発性」と「変異性」と類似している。

報告企業の意見	今後の対応
本実験結果から，TSE に関与するプリオンは当初考えられていた以上に多様性に富み，またヒトへの感染はプリオンの種類によって異なることが示唆された。これは，ウシ由来製品を含有する血漿分画製剤の製造工程におけるプリオン除去工程を評価する際に考慮が必要となる可能性がある。	弊社の血漿分画製剤の製造工程において，これまでに同定されている種々のウシプリオンに対してプリオン除去工程は効果的であることが確認されている。 現時点で新たな安全対策上の措置を講じる必要はないと考える。引き続き関連情報の収集に努める。

使用上の注意記載状況・その他参考事項等

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www.elsevier.com/locate/vaccine

Atypical transmissible spongiform encephalopathies (TSEs) in ruminants

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Abstract

Transmissible spongiform encephalopathies (TSEs) are associated with the accumulation in infected tissues of a disease-associated form of a host-encoded protein, the prion protein (PrP). Contrary to the normal form of the protein, this form of PrP is partially resistant to protease digestion (PrP^{res}). Detailed characterisation of PrP^{res} has been intensively investigated in recent years to try and decipher the diversity of TSEs in human and animals. This considerably and unexpectedly enlarged our knowledge about such diseases in ruminants. Previously, such a diversity was essentially shown by the demonstration that scrapie from sheep and goats could have different biological behaviours following transmission of the disease in mice, unlike bovine spongiform encephalopathy from cattle (BSE) which showed a distinct and unique behaviour. The properties of the BSE agent were also demonstrated to be very stable, following transmission to a variety of different species. Molecular studies of PrP^{res}, followed by transmission studies to mice, gave the first evidence for the accidental transmission of the BSE agent to humans where it induced a variant form of the fatal Creutzfeldt-Jakob disease (CJD) and also to different animal species including a goat in France. This last case was found among a few unusual cases of TSEs in small ruminants that showed some molecular similarities with BSE and which are currently under investigation by transmission studies in mice. The application of the molecular methods to characterise PrP^{res} has most recently led to the unexpected discovery of deviant BSE forms in a few affected cattle in Europe and in the United States, which raises the question of a possible different origin at least of some cases of BSE in cattle. Finally, considerable numbers of a new TSE form in small ruminants, referred to as "atypical scrapie" or "Nor98", have meanwhile been identified in most European countries by TSE rapid testing using an assay which recognizes also comparatively less PK resistant PrP^{res}.

Keywords: Atypical; BSE; Scrapie; Prion; Strain

1. Introduction

Transmissible spongiform encephalopathies (TSEs) are fatal neuro-degenerative diseases, affecting both human (Creutzfeldt-Jakob disease; CJD) and animals, including mainly sheep and goats (scrapie), deer and elk (chronic wasting disease; CWD) and cattle (bovine spongiform encephalopathy; BSE). The exact nature of the infectious agent involved in the transmission of these diseases remains controversial. However, a central event in their pathogenesis is the accumulation in infected tissues of an abnormal form of a host-encoded protein, the prion protein (PrP) [1,2]. Whereas the normal cellular protein is fully sensitive to proteases (PrP^{sen}), the disease-associated prion protein (PrP^{d}) is only partly degraded (PrP^{res}), its amino-terminal end being removed.

Experimental transmissions of these diseases, especially that of scrapie from small ruminants, revealed a biological diversity of the involved infectious agent, reminiscent of "strains" among classical infectious agents, like viruses [3]. This has been mainly described in genetically defined inbred wild-type mice, by the different features of the disease between different strains, including differences in the

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incubation periods and in the distribution of brain lesions; these features remained generally remarkably stable following serial passages of a given strain in a given mouse model [4,5].

Distinct and specific features of the PrP^{res} protein, as characterised in most studies by Western blot methods, have also been found in mice or in hamsters infected with different biological strains of TSE agents, suggesting that biological properties of the infectious agent might be enciphered in the conformation of the disease-associated form of the prion protein [6–12].

2. Search for the possible presence of BSE in small ruminants with natural TSEs

Characterisation of the infectious agent associated with BSE showed unique features, with characteristic incubation periods of the disease, as well as a defined distribution and nature of brain lesions, following transmission of the disease in wild-type mouse lines [13–16]. Studies of brain lesions essentially involved the histological analysis of the distribution and intensity of spongiform changes in precise neuro-anatomical sites, but can also rely on the neuro-anatomical mapping of PrP^{d} by PET-blot method and/or immunohistochemistry [15–17]. Such features assessed by bioassay in mice remained unchanged following transmission of the BSE agent after passages from cattle to other species [5,14,15,17].

Western blot analyses of PrP^{res} accumulating in the brains of BSE-infected animals and humans have also demonstrated specific molecular features, compared to most other cases of prion diseases found in the same species, with a lower apparent molecular mass of the unglycosylated PrP^{res} moiety and very high proportions of diglycosylated PrP^{res} [18,19] (Fig. 1). This lower apparent molecular mass in BSE has been linked to a particular proteinase K cleavage, leading to a possible discrimination from most scrapie sources by differential PrP^{res} labelling with different antibodies against different regions of the PrP protein; this was indeed associated with a specific loss of PrP^{res} immunoreactivity with certain monoclonal antibodies that recognize a particular region of the protein which is specifically digested in BSE (for instance P4 or 12B2 antibodies recognising the 93-WGQGG-97 amino-acids sequence in the sheep PrP) [8,20–23]. Similar molecular discrimination between BSE and scrapie in small ruminants was also obtained using immunohistochemical methods for mapping of PrP^{d} cellular cleavage [24–27].

Such findings have allowed the research of a possible transmission of the BSE agent in natural field conditions in animals, such as in sheep and goats. This recently led to the identification in France of a first case of TSE in a goat (CH636) with PrP^{res} molecular properties similar to that found in BSE [28]. Characterisation of the infectious agent by transmission studies in mice confirmed, by analysis of the incubation periods of the disease and of the distribution of brain lesions, that it was undistinguishable from the cattle BSE agent. More recently, molecular similarities between a natural TSE case identified in a goat in the UK were also reported, although bioassay has not yet been completed to confirm the isolation of the BSE agent in this case [25].

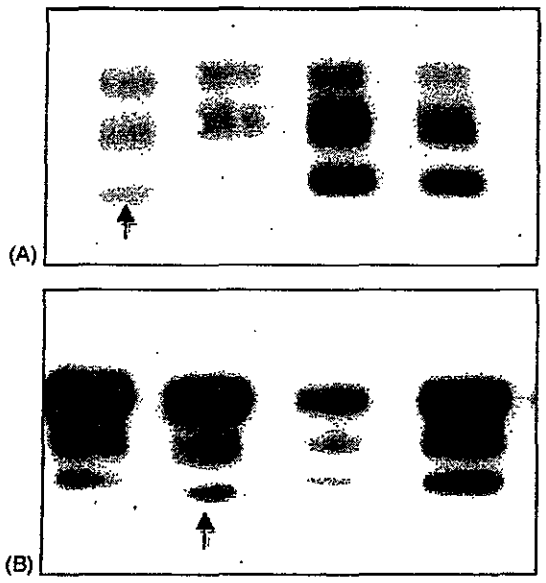

Fig. 1. Western blot detection of PrP^{res} in BSE (arrow) compared to three scrapie sources, in C57Bl/6 mice (panel A) or in sheep (panel B). The lower band corresponding to the unglycosylated PrP^{res} shows a lower apparent molecular mass in BSE-infected animals.

However, as early as 1999, it was shown that some scrapie isolates could also show very close PrP^{res} Western blot patterns to that found in experimental ovine BSE [29]. This was demonstrated in an historical British scrapie isolate, CH1641 that had been used in scrapie transmission experiments in sheep. In this case, although subtle differences with ovine BSE might be found by Western blot [21,22], the apparent molecular masses of unglycosylated PrP^{res} were hardly distinguishable between CH1641 and ovine BSE. Immunohistochemical approach could show that, in sheep infected with the CH1641 isolate, PrP^{d} in neurones differs from BSE in having an even longer segment of the N-terminus digested by intracellular enzymes [26]. The biological properties of the infectious agent associated with this CH1641 experimental scrapie isolate are clearly distinct from BSE, since, contrary to BSE, it consistently failed to be transmitted to wild-type mice [30].

A few other TSEs isolates with close PrP^{res} molecular properties by Western blot to that found in ovine BSE have been identified, although these showed different features in immunohistochemistry compared to experimental ovine BSE [27]. Such isolates are currently under investigation by transmission in mice. First results led to puzzling observations following transmission in a transgenic mouse line (TgOv-PrP4) that over-express the ovine PrP protein (A136 R154 Q171 sequence) [31] and that was shown to faithfully repro-

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