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No. 23

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2009. 12. 25	該当なし	
一般的名称	新鮮凍結人血漿		研究報告の公表状況	UK Department of Health, Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO). Available from: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_108860.pdf	公表国 英国	
販売名(企業名)	新鮮凍結血漿「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」成分採血(日本赤十字社)					

研究報告の概要 180

○英国血液・組織・臓器の安全性にかかる諮問委員会 2009年10月27日第8回会議議事要旨 プリオンフィルターについて
メンバーはこれまでの会議でプリオンフィルターについて議論を重ね、有効性と安全性双方の分析について最新の情報を入手してきた。この情報は、プリオンフィルター処理赤血球の安全性を分析する臨床試験(the PRISM trial)及び製剤についての個別の有効性分析から得られ、ワーキンググループメンバーに報告された。臨床試験の初期結果は有望だったが、完了までまだ時間がかかることを指摘した。メンバーはメーカーと他の研究から得られた情報に加えて、保健省の有効性評価のデータを評価した。動物を使用した内部の有効性試験からデータが得られるのは2014年になる。
以上の情報と分析から委員会は以下の通り結論する。
・プリオンの感染性を低減させるフィルターに今では十分なエビデンスがあることを確信している。
・1996年1月1日以降に生まれた人には、PRISM臨床試験の完了を条件としてフィルター処理赤血球を使用すること。
委員会は、プリオンフィルター処理が実施された場合、フィルターの普及率や有効性についてさらにデータが得られた場合は見直しを行うとした。
委員会はこれまでに、vCJDリスク対策として、16歳未満の患者とヘモグロビン上昇患者には2倍量赤血球(DDRC)を使用するよう推奨していた。プリオンフィルター処理赤血球を使用する患者については、DDRCの推奨は撤回される。

使用上の注意記載状況・その他参考事項等

新鮮凍結血漿「日赤」
新鮮凍結血漿-LR「日赤」
新鮮凍結血漿-LR「日赤」成分採血

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

報告企業の意見	今後の対応
英国の血液・組織・臓器の安全性にかかる諮問委員会で、1996年1月1日以降に生まれた人の輸血にプリオンフィルター処理赤血球を使用することが推奨されたとの報告である。	日本赤十字社は、vCJDの血液を介する感染防止の目的から、献血時に過去の海外渡航歴(旅行及び居住)を確認し、1980～96年の英国1ヶ月をはじめ、欧州等38ヶ国に一定期間滞在したドナーを無期限に献血延期としている。今後もCJD等プリオン病に関する新たな知見及び情報を収集するとともに、血漿分画製剤の製造工程における病原因子の除去・不活化技術の向上に努める。

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SaBTO

Advisory Committee on the Safety of Blood, Tissues and Organs

Summary of the Eighth Meeting, 27 October 2009

1. Consent for blood transfusion

Members were reminded that questionnaires regarding informed consent for blood transfusion had been finalised by a working group consisting of SaBTO members and other experts. Two questionnaires have been developed which are specifically for either Healthcare Professionals or Patient groups. The working group had agreed the management of the consultation process with the Department of Health. The consultation process will be UK wide. Participants will be given 12 weeks to respond, after which time the consultation will close and the responses will be analysed.

2. MSBTO Guidance update

Members noted the urgent need for this update, which was expected to be forthcoming shortly.

3. Prion Filtration

Members had discussed prion filtration at previous meetings, and had asked to be kept updated on progress of both efficacy and safety assessments. This was provided via a presentation from the vCJD working group, with new data from both the ongoing clinical trial to assess safety of prion filtered red blood cells (the PRISM trial) and independent efficacy assessments of the performance of the same product. Early results from the clinical trial are encouraging, but members noted that the trial is still some way from completion. Members were appraised of data from the Health Protection Agency's independent evaluation of efficacy, in addition to information from the manufacturer and another independent study. The committee noted that independent data from animal based, endogenous studies of efficacy will not be available until 2014.

Having considered the information and analysis provided, the committee:

- is satisfied that there is now sufficient evidence that this particular filter reduces infectivity;
- recommends that filtered red cells be provided to those born since 1 January 1996, subject to satisfactory completion of the PRISM clinical trial.

The committee also noted that, if implemented, the continuing requirement for prion filtration should be reviewed in the event that either further data on prevalence or efficacy of the filters becomes available.

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JRC2009T-066

The committee had previously recommended the introduction of double dose red cells (DDRC) as a vCJD risk-reduction measure for under 16s and patients with haemoglobinopathies. SaBTO recommended that DDRC be rescinded for those groups receiving prion filtered blood.

B　個別症例報告概要

○　総括一覧表
○　報告リスト

個別症例報告のまとめ方について

個別症例報告が添付されているもののうち、個別症例報告の重複を除いたものを一覧表の後に添付した（国内症例については、資料3において集積報告を行っているため、添付していない）。

感染症定期報告の報告状況(2010/3/1～2010/5/31)

血対課ID	受理日	番号	報告者名	一般名	生物由来成分名	原材料名	原産国	含有区分	文献	症例	適正使用調査
100113	2010/3/29	91089	CSLベーリング	フィブリノゲン加第XIII因子	アンチトロンビン	ヒト血液	米国、ドイツ、オーストリア	製造工程	有	有	無
100114	2010/3/29	91090	CSLベーリング	人血清アルブミン 人血液凝固第XIII因子 フィブリノゲン加第XIII因子	人血清アルブミン	ヒト血液	米国、ドイツ、オーストリア	有効成分添加物	有	有	無
100115	2010/3/29	91091	CSLベーリング	フィブリノゲン加第XIII因子	アプロチニン液	ウシ肺	ウルグアイ、ニュージーランド	有効成分	無	有	無
100116	2010/3/29	91092	CSLベーリング	フィブリノゲン加第XIII因子	トロンビン末	ヒト血液	米国、ドイツ、オーストリア	有効成分	有	有	無
100117	2010/3/29	91093	CSLベーリング	フィブリノゲン加第XIII因子	フィブリノゲン	ヒト血液	米国、ドイツ、オーストリア	有効成分	有	有	無
100119	2010/3/30	91096	バクスター	乾燥濃縮人血液凝固第VIII因子	乾燥人血液凝固第VIII因子	人血漿	米国	有効成分	無	有	無
100120	2010/3/30	91097	バクスター	乾燥濃縮人血液凝固第VIII因子	人血清アルブミン	人血漿	米国	添加物	無	有	無
100127	2010/4/15	100065	CSLベーリング	フィブリノゲン加第XIII因子 人血液凝固第XIII因子	人血液凝固第XIII因子	ヒト血液	米国、ドイツ、オーストリア	有効成分	有	有	無
100128	2010/4/15	100066	CSLベーリング	抗破傷風人免役グロブリン	破傷風抗毒素	ヒト血液	米国、ドイツ、オーストリア	有効成分	有	有	無
100144	2010/4/23	100124	バクスター	人血清アルブミン	人血清アルブミン	人血漿	米国	有効成分	無	有	無

感染症発生症例一覧

	番号	感染症の種類 器官別大分類	感染症の種類 基本語	発生国	性別	年齢	発現時期	転帰	出典	区分	備考
第14回	1	感染症および寄生虫症	A型肝炎	ドイツ	女	71	2009/12/14	不明	症例報告	外国製品	識別番号3-09000024 報告日:2010年2月8日
第14回	1	感染症および寄生虫症	B型肝炎	ドイツ	女	71	2009/12/14	不明	症例報告	外国製品	識別番号3-09000024 報告日:2010年2月8日
第14回	1	感染症および寄生虫症	C型肝炎	ドイツ	女	71	2009/12/14	不明	症例報告	外国製品	識別番号3-09000024 報告日:2010年2月8日
第13回	報告なし										
第12回	1	感染症および寄生虫症	HIV感染	ドイツ	男	35	不明	不明	症例報告	外国製品	識別番号3-08000029 報告日:2009年02月17日
第12回	1	感染症および寄生虫症	B型肝炎	ドイツ	男	35	不明	不明	症例報告	外国製品	識別番号3-08000029 報告日:2009年02月17日
第12回	2	感染症および寄生虫症	C型肝炎	ドイツ	女	77	2009/1/5	不明	症例報告	外国製品	識別番号3-08000039 報告日:2009年02月17日
第11回	1	臨床検査	C型肝炎抗体陽性	日本	女	37	2007/9/11	不明	症例報告	当該製品	識別番号1-07000251 報告日:2008年4月30日
第11回	2	感染症および寄生虫症	C型肝炎	ドイツ	女	60	2007/4/13	不明	症例報告	外国製品	識別番号3-08000005 報告日:2008年5月29日
第10回	1	感染症および寄生虫症	B型肝炎	ドイツ	男	24	2008/1/10	不明	症例報告	外国製品	識別番号3-07000026 報告日:2008年4月1日
第10回	2	感染症および寄生虫症	B型肝炎	日本	女	33	2007/8/7	回復	症例報告	当該製品	識別番号1-07000093 報告日:2007年10月11日
第9回	報告なし										
第8回	1	感染症および寄生虫症	C型肝炎	ドイツ	女	41	2006/11/21	不明	症例報告	外国製品	識別番号3-06000029 報告日:2006年12月20日
第8回	1	臨床検査	C型肝炎抗体陽性	ドイツ	女	41	2006/11/21	不明	症例報告	外国製品	識別番号3-06000029 報告日:2006年12月20日
第8回	1	臨床検査	C型肝炎RNA陽性	ドイツ	女	41	2006/11/21	不明	症例報告	外国製品	識別番号3-06000029 報告日:2006年12月20日
第7回	1	感染症および寄生虫症	C型肝炎	ドイツ	女	63	2005年11月	不明	症例報告	外国製品	識別番号:3-06000004 報告日:2006年5月18日
第6回	1	感染症および寄生虫症	B型肝炎	ドイツ	男	74	2005/10/21	死亡	症例報告	外国製品	識別番号:3-05000494 報告日:2005年12月27日
第6回	1	感染症および寄生虫症	輸血後肝炎	ドイツ	男	74	2005/10/21	死亡	症例報告	外国製品	識別番号:3-05000494 報告日:2005年12月27日
第6回	1	臨床検査	抗HBs抗体陽性	ドイツ	男	74	2005/10/21	死亡	症例報告	外国製品	識別番号:3-05000494 報告日:2005年12月27日
第6回	2	感染症および寄生虫症	B型肝炎	ドイツ	女	77	2005/9/28	未回復	症例報告	外国製品	識別番号:3-05000493 報告日:2005年12月27日
第5回	1	感染症および寄生虫症	ウイルス性肝炎	ドイツ	女	55	1995年	不明	症例報告	外国製品	識別番号:3-04000122 報告日:2005年6月8日
第4回	1	臨床検査	C型肝炎陽性	フランス	男	68	2004/08	不明	症例報告	外国製品	識別番号:3-04000088 報告日:2004年11月22日
第3回	報告なし										
第2回	報告なし										

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2010. 1. 19	該当なし	
一般的名称	人血清アルブミン				公表国	
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 赤十字アルブミン20%静注4g/20mL(日本赤十字社) 赤十字アルブミン20%静注10g/50mL(日本赤十字社) 赤十字アルブミン25%静注12.5g/50mL(日本赤十字社)		研究報告の公表状況	Kaski D, Mead S, Hyare H, Cooper S, Jampana R, Overell J, Knight R, Collinge J, Rudge P. Lancet. 2009 Dec 19;374(9707):2128.	英国	

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○コドン129ヘテロ接合性の変異型CJD患者

30歳男性が、13ヶ月前から人格変化、進行性不穏、知能低下を呈し、2008年6月に入院した。患者は重度下肢痛および記憶低下を訴えた。2ヵ月後、幻視を発現し、腹部に腫瘍があるという妄想を持った。その後3ヶ月間に症状は悪化し、2008年10月の精神状態検査のスコアは26/30であった。追跡眼球運動は衝動性であり、口とがらし反射があった。腕に軽度運動失調があり、下肢には腱反射亢進と左足底伸展反応を伴う重度失調があった。歩行に2本の杖を必要とした。既往歴には、頸部リンパ節除去および扁桃摘出術(15年前)があったが、輸血歴やヒト組織の移植歴はなかった。EEGは徐波活性を示した。CSFのタンパク、ブドウ糖、血球数は正常であったが、14-3-3タンパク質が陽性であった。脳MRI所見は、視床枕徴候と一致した。評価したすべての神経放射線医が視床枕徴候を陽性と見なしたわけではないが、定量評価で尾状核と比べ視床枕核の高い対称性信号が示された。遺伝性、代謝性、自己免疫性疾患(腫瘍誘発性疾患を含む)の広範なスクリーニング検査結果は陰性であった。PRNP解析は、既知疾患に関連する突然変異を示さなかった。コドン129はヘテロ接合性だった。特徴的臨床症状、疾患の進行、他の診断の除外、ならびにMRI所見に基づき、変異型クロイツフェルトヤコブ病(vCJD)の臨床診断が下された。患者の年齢が若く、臨床症状、MRI所見、ならびにEEGでpseudoperiodic complexesが見られないことを複合的に考慮し、孤発性CJDの可能性は低いと判断した。患者の保護者はそれ以上の検査は望まなかった。患者の容態は悪化し、2009年1月に死亡した。剖検は実施されなかった。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25
赤十字アルブミン20%静注4g/20mL
赤十字アルブミン20%静注10g/50mL
赤十字アルブミン25%静注12.5g/50mL

血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
プリオンタンパク遺伝子コドン129はヘテロ接合性で、臨床症状、疾患の進行、他の診断の除外、MRI所見から変異型クロイツフェルトヤコブ病と診断された患者の症例報告である。 プリオン病の原因とされる異常プリオンがコーン分画工程で効果的に除去されるとの成績と併せて、これまでの疫学研究では如何なるプリオン病も、アルブミンを介して伝播するという証拠は無い。また本製剤の使用は一時的かつ限定的であることから伝播のリスクは非常に低いものと考える。	日本赤十字社は、vCJDの血液を介する感染防止の目的から、献血時に過去の海外渡航歴(旅行及び居住)を確認し、欧州36ヶ国に一定期間滞在したドナーを無期限に献血延期としている。また、英国滞在歴を有するvCJD患者が国内で発生したことから、平成17年6月1日より1980～96年に1日以上の英国滞在歴のある人の献血を制限している。今後もCJD等プリオン病に関する新たな知見及び情報を収集するとともに、血漿分画製剤の製造工程における病原因子の除去・不活化技術の向上に努める。

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MedDRA/J Ver.12.0J

JRC2010T-003

Case Report

Variant CJD in an individual heterozygous for PRNP codon 129

Diego Kaski, Simon Mead, Harpreet Hyare, Sarah Cooper, Ravi Jampana, James Overell, Richard Knight, John Collinge, Peter Rudge

Lancet 2009; 374: 2128

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A 30-year-old man was admitted to hospital in June, 2008, with a 13-month history of personality change, progressive unsteadiness, and intellectual decline. He complained of severe leg pain and poor memory. 2 months later he developed visual hallucinations and falsely believed he had an abdominal tumour. Symptoms worsened over the next 3 months. In October, 2008, his score on the mini mental state examination was 26/30. Pursuit eye movements were saccadic. He had a pout reflex. There was mild ataxia in the arms. His legs were severely ataxic with brisk tendon reflexes and a left extensor plantar response. He needed two crutches to walk. Medical history included tonsillectomy and removal of a cervical lymph node 15 years previously but he had never had a blood transfusion or received implantation of other human tissues.

EEG showed slow wave activity. CSF protein, glucose, and cell count were normal but the 14-3-3 protein was positive. MRI of the brain was consistent with the pulvinar sign (figure A). Although not all neuroradiologists consulted considered the pulvinar sign positive, quantitative assessment showed symmetrical higher signal in the pulvinar nuclei than the caudate nuclei (figure B). Extensive screens for genetic, metabolic, and autoimmune diseases, including those induced by neoplasia, were negative. *PRNP* analysis did not show any known disease-associated mutations; codon 129 was heterozygous. A clinical diagnosis of variant Creutzfeldt-Jakob disease (vCJD) was made on the basis of a characteristic clinical onset and progression, exclusion of other diagnoses, and MRI findings. Sporadic CJD was judged unlikely given the combination of young age, clinical features, MRI findings, and absence of pseudoperiodic complexes on EEG. His carers did not want further investigation. His condition deteriorated and he died in January, 2009. Autopsy was not done.

Human prion diseases have acquired, sporadic, and inherited aetiologies, show wide phenotypic heterogeneity, and are associated with propagation of infectious prions of many distinct strain types.[1] Since 1994, about 200 cases of vCJD, causally related to exposure to bovine spongiform encephalopathy (BSE) prions, have been identified worldwide. vCJD is generally seen in young adults, has characteristic neuropathological features and tissue distribution of infectivity, and a distinctive type 4 (London classification) molecular strain type.[1] A polymorphism at codon 129 (encoding methionine or valine) of the human prion protein gene (*PRNP*), constitutes a powerful susceptibility factor in all types of prion disease. In vCJD, every case genotyped to date has been methionine homozygous,[2] the other acquired prion diseases, cases have occurred in all genotypes but with different mean incubation periods,[1] which can span decades.[3] *PRNP* codon 129 heterozygotes generally have the longest incubation periods. There is a report of a recipient of a blood transfusion from a donor incubating vCJD who died of unrelated causes but showed signs of prion infection at autopsy and was *PRNP* codon 129 heterozygous.[4] Animal studies have suggested that different clinicopathological phenotypes could occur in people with various *PRNP* codon 129 genotypes.[4,5] The majority of the UK population have potentially been exposed to BSE prions but the extent of clinically silent infection remains unclear. About a third of the UK population are *PRNP* codon 129 methionine homozygous. If individuals with other genotypes are similarly susceptible to developing prion disease after BSE prion exposure, but with longer incubation periods, further cases, which may or may not meet diagnostic criteria for vCJD, would be expected in these *PRNP* codon 129 genotypes. However, prion disease susceptibility and incubation periods are also affected by other genetic loci, and the possibility remains that cases of vCJD to date may have unusual combinations of genotypes at these loci, yet to be fully characterised.

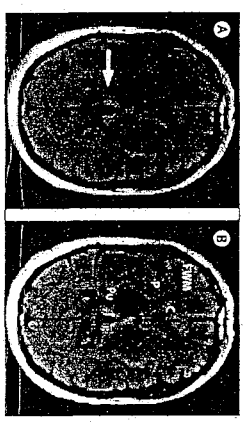

Figure: MRI

(A) Increased signal intensity in the pulvinar nucleus bilaterally (arrow). (B) MR signal intensity in the pulvinar (Pu) is higher than in the head of the caudate nuclei (C), putamen (P), and right frontal white matter (FWM).

Contributors

All authors were involved in discussion about diagnosis, care of the patient, and preparation of the report. Written consent to publish was obtained.

Conflicts of interest

JC is a director and shareholder of D-Gen Ltd, an academic spin-out company in the field of prion disease diagnosis, decontamination, and therapy. The other authors declare that they have no conflicts of interest.

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医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2010. 1. 15	該当なし	
一般的名称	人血清アルブミン		研究報告の公表状況	ProMED. 20100107.0076, 2010 Jan 07. 情報源:UK: National CJD Surveillance Unit - monthly statistics as of 5 Jan 2010.	公表国 英国	
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社) 赤十字アルブミン20%静注4g/20mL(日本赤十字社) 赤十字アルブミン20%静注10g/50mL(日本赤十字社) 赤十字アルブミン25%静注12.5g/50mL(日本赤十字社)					

研究報告の概要 170

○プリオン病最新情報 英国:国立CJDサーベイランスユニット、月次vCJD・CJD統計、2010年1月5日時点
英国のCJDサーベイランスユニットから公表されたvCJDを始めとするプリオン病の患者数に関する最新情報である。
vCJD確定例または可能性例総数は前月から変化なく166名のままである。生存患者は4名であるため、2009年までのvCJD症例数は合計170例である。
2009年中に新たに2症例が記録されたが、全体としては英国におけるvCJD流行は減少しつつあるとする見解に一致している。
vCJDによる死亡患者は1995年に初めて確認され、死亡患者数のピークは2000年の28名であった。その後2001年に20名、2002年に17名、2003年に18名、2004年に9名、2005年に5名、2006年に5名、2007年に5名、2008年に1名、2009年に2名となっている。
プリオン病患者全体としては、2009年の12ヶ月間に143名の照会があった。このうち、孤発性CJD:59名、家族性CJD:1名、医原性CJD:1名、GSS:3名、vCJD:2名だった。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25
赤十字アルブミン20%静注4g/20mL
赤十字アルブミン20%静注10g/50mL
赤十字アルブミン25%静注12.5g/50mL

血液を原料とすることに由来する感染症伝播等

報告企業の意見

英国CJDサーベイランスユニットの統計によると、2010年1月5日の時点でvCJD死亡患者総数は170名であり、英国におけるvCJD流行は収まりつつあるとする見解に一致するとの報告である。
プリオン病の原因とされる異常プリオンがコーン分画工程で効果的に除去されるとの成績と併せて、これまでの疫学研究では如何なるプリオン病も、アルブミンを介して伝播するという証拠は無い。また本製剤の使用は一時的かつ限定的であることから伝播のリスクは非常に低いものと考える。

今後の対応

日本赤十字社は、vCJDの血液を介する感染防止の目的から、献血時に過去の海外渡航歴(旅行及び居住)を確認し、欧州36ヶ国に一定期間滞在したドナーを無期限に献血延期としている。また、英国滞在歴を有するvCJD患者が国内で発生したことから、平成17年6月1日より1980～96年に1日以上の英国滞在歴のある人の献血を制限している。今後もCJD等プリオン病に関する新たな知見及び情報を収集するとともに、血漿分画製剤の製造工程における病原因子の除去・不活化技術の向上に努める。

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MedDRA/J Ver.12.0J

[in French, trans. & summ. Mod.CP]
<http://www.invs.sante.fr/display/?doc=publications/mcj/donnees_mcj.html>

During the 12 months of 2009, there were 1486 referrals, 85 cases of sporadic CJD, 10 cases of familial CJD, 3 cases of iatrogenic CJD, and 2 confirmed cases of vCJD.

A total of 25 cases of confirmed or probable vCJD has now been recorded in France since 1997. The 25 confirmed cases comprise 13 females and 12 males. All 25 are now deceased. Their median age is 37 (between 19 and 58). Seven were resident in the Ile-de-France and 18 in the provinces. All the identified cases have been Met-Met homozygotes. No risk factor has been identified. One of the 25 had made frequent visits to the United Kingdom.

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[3] US National Prion Disease Center - not updated since 7 Nov 2009
Date: Sat 7 Nov 2009
Source: US National Prion Disease Pathology Surveillance Center [edited]
<http://www.cjdsurveillance.com/pdf/case-table.pdf>

(Report not updated since 7 Dec 2009): During the period 1 Jan 2009 to 7 Nov 2009, there were 341 referrals, of which 198 were classified as Prion disease, comprising 133 cases of sporadic CJD, 33 of familial CJD, and no cases of iatrogenic CJD or vCJD.

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[4] Portuguese vCJD case - pathology
Date: Fri 1 Jan 2010
Source: J Neurol Neurosurg Psychiatry 2010 Jan;81(1):112-4. [edited]
<http://jnnp.bmj.com/content/81/1/112.abstract>

Title: Variant Creutzfeldt-Jakob disease: the first confirmed case from Portugal shows early onset, long duration and unusual pathology.

Authors: Barbot C, Castro L, Oliveira C, Carpenter S.
At: Department of Neuropaediatrics, Hospital Maria Pia, Porto, Portugal.

Summary:
We present clinical and autopsy findings in the 1st case of variant Creutzfeldt-Jakob disease diagnosed and confirmed in Portugal. Onset was at 11 years, the earliest onset reported, and the course (32 months) relatively long. Western blot showed protease resistant prion protein, mainly of type 4 (2B) isoform. The cerebral cortex revealed severe spongiform change with numerous amyloid plaques, which did not fit the definition of florid plaques. In the striatum, spongiform change was limited, but the extracellular space was dilated. Other reports have found marked spongiform change in the striatum and little in the cortex. Massive neuronal loss, in excess of what has been described, was found in the thalamus and pontine grey. The cerebellum showed, as expected, severe loss of granule cells, moderate loss of Purkinje cells and marked immunopositivity for the prion protein. Differences between our findings and previous ones probably result from the patient's long survival.

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Terry S. Singeltary Sr. <flounder9@verizon.net>

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[5] vCJD codon 129 heterozygote
Date: Fri 19 Dec 2009
Source: BBC News, Health [edited]
<http://news.bbc.co.uk/1/hi/health/8419459.stm>

A 30-year-old man thought to have died in January [2009] from vCJD belonged to a genetic group that had not shown any signs of the disease, scientists say. In the UK, 166 people have died of vCJD, linked to eating BSE [bovine spongiform encephalopathy] infected beef, and all were thought to have shared a certain gene.

Writing in the Lancet, scientists say that the victim, a resident of, Lanarkshire [Scotland], had a different version of the gene. They estimate that up to 350 people in this group could get vCJD. Scientists have always thought that a 2nd wave of vCJD cases would emerge some time after the 1st. This is the 1st indication that this theory is being born out, with the identification of the 1st probable vCJD patient outside of the initial genetic group, BBC science correspondent Pallab Ghosh reports.

The father believes his son was incubating the disease for much of his life. It is probable because the diagnosis is based on observations of the progression of the disease rather than post-mortem tests which would have provided absolute confirmation of the disease, he adds.

The case report written by Professor John Collinge of the National Prion Clinic and colleagues is a reminder that the disease has not gone away. Many thousands of people may be carrying the infection, and although they will never show any symptoms, they have the potential to infect others.

vCJD is caused by infectious agents called prions. Prion diseases affect the structure of the brain or other neural tissue and are currently untreatable. Disease-causing prions are thought to consist of abnormally folded proteins, which spread by encouraging the normal healthy prion protein found on the surface of most cells in the body to change shape. Tests showed that the patient had a heterozygous version of the gene which codes for the human prion amino acids valine (V) or methionine (M). People can be V V (homozygous), M M (homozygous) or M V (heterozygous). Since 1994, around 200 cases of vCJD have been identified worldwide, and all those tested have been M M homozygous. [However, genetic analysis of 2 out of 3 prion-positive appendix samples in the tissue-based prevalence study in 2001-2004 showed that both were valine homozygous (VV) at codon 129 in the prion protein gene (Ironside et al, Brit Med J 2006). - Mod.CP]. However, this most recent victim was M/V heterozygous. It is thought that 47 percent of the population have this version of the gene. Professor Collinge said: "The majority of the UK population have potentially been exposed to BSE prions, but the extent of clinically silent infection remains unclear. About 1/3rd of the UK population are M/M homozygous. If individuals with other genotypes [M/V and V/V] are similarly susceptible to developing prion disease after BSE prion exposure, but with longer incubation periods, further cases would be expected."

The scientists have previously looked at another prion disease in New Guinea called "kuru" [which was induced by eating infected human brain tissue. - Mod.CP]. The original cases were all M/M, but more recently, M/V cases have appeared. They say this indicates that M/V people can get prion diseases like kuru but have a much longer incubation period.

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[The abstract of the Lancet paper upon which the above report is based is reproduced below. - Mod.CP]

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[6] vCJD codon 129 heterozygote - Lancet paper
Date: Thu 18 Dec 2009
Source: Lancet 2009; 374: 2128 [edited]
<http://press.thelancet.com/vcjd.pdf>

[A Case Report published in the 18 Dec 2009 issue of the Lancet by Professor John Collinge, MRC Prion Unit and National Prion Clinic,

UCL Institute of Neurology and National Hospital for Neurology and Neurosurgery, London]

A 30-year-old man was admitted to hospital in June 2008 with a 13-month history of personality change, progressive unsteadiness, and intellectual decline. He complained of severe leg pain and poor memory. Two months later, he developed visual hallucinations and falsely believed he had an abdominal tumour. Symptoms worsened over the next 3 months. In October 2008, his score on the mini mental state examination was 26/30. Pursuit eye movements were saccadic [a rapid movement of the eye between fixation points]. He had a pout reflex. There was mild ataxia in the arms. His legs were severely ataxic with brisk tendon reflexes and a left extensor plantar response. He needed 2 crutches to walk. Medical history included tonsillectomy and removal of a cervical lymph node 15 years previously, but he had never had a blood transfusion or received implantation of other human tissues.

EEG showed slow wave activity. CSF protein, glucose, and cell count were normal, but the 14-3-3 protein was positive. MRI [magnetic resonance imaging] of the brain was consistent with the pulvinar sign (illustrated in the original text). Although not all neuroradiologists consulted considered the pulvinar sign positive, quantitative assessment showed symmetrical higher signal in the pulvinar nuclei than the caudate nuclei (illustrated in the original text). Extensive screens for genetic, metabolic, and autoimmune diseases, including those induced by neoplasia, were negative. PRNP analysis did not show any known disease-associated mutations; codon 129 was heterozygous. A clinical diagnosis of variant Creutzfeldt-Jakob disease (vCJD) was made on the basis of a characteristic clinical onset and progression, exclusion of other diagnoses, and MRI findings. Sporadic CJD was judged unlikely given the combination of young age, clinical features, MRI findings, and absence of pseudoperiodic complexes on EEG. His care givers did not want further investigation. His condition deteriorated, and he died in January 2009. Autopsy was not done.

Human prion diseases have acquired, sporadic, and inherited aetiologies, show wide phenotypic heterogeneity, and are associated with propagation of infectious prions of many distinct strain types (1). Since 1994, about 200 cases of vCJD, causally related to exposure to bovine spongiform encephalopathy (BSE) prions, have been identified world-wide. vCJD is generally seen in young adults, has characteristic neuropathological features and tissue distribution of infectivity, and a distinctive type 4 (London classification) molecular strain type (1). A polymorphism at codon 129 (encoding methionine or valine) of the human prion protein gene (PRNP) constitutes a powerful susceptibility factor in all types of prion disease. In vCJD, every case genotyped to date has been methionine homozygous. In the other acquired prion diseases, cases have occurred in all genotypes but with different mean incubation periods (1), which can span decades (2); PRNP codon 129 heterozygotes generally have the longest incubation periods. There is a report of a recipient of a blood transfusion from a donor incubating vCJD who died of unrelated causes but showed signs of prion infection at autopsy and was PRNP codon 129 heterozygous (3). Animal studies have suggested that different clinicopathological phenotypes could occur in people with various PRNP codon 129 genotypes (4,5). The majority of the UK population have potentially been exposed to BSE prions but the extent of clinically silent infection remains unclear. About 1/3rd of the UK population are PRNP codon 129 methionine homozygous. If individuals with other genotypes [V/V or V/M] are similarly susceptible to developing prion disease after BSE prion exposure, but with longer incubation periods, further cases, which may or may not meet diagnostic criteria for vCJD, would be expected in these PRNP codon 129 genotypes. However, prion disease susceptibility and incubation periods are also affected by other genetic loci, and the possibility remains that cases of vCJD to date may have unusual combinations of genotypes at these loci, yet to be fully characterised.

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(3) Peden AH, Head MW, Ritchie DL, Bell JE, Ironside JW. Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. Lancet 2004; 364: 527-29.

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[Acknowledgment: MRC Prion Unit and National Prion Clinic, UCL Institute of Neurology and National Hospital for Neurology and Neurosurgery, London, UK (D Kaski MRCP, S Mead PhD, H Hyare FRCR, Prof J Collinge FRS, P Rudge FRCP); Institute of Neurological Sciences, Glasgow University, Glasgow, UK (S Cooper MRCP, R Jampana FRCR, J Overell FRCP); and National CJD Surveillance Unit, Western General Hospital, Edinburgh, UK (Prof R Knight FRCP)]

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[To put this work in perspective, parts of a British Medical Journal editorial by Maurizio Pocchiari are reproduced below. - Mod.CP.

Date: 21 May 2009
Source: BMJ 2009;338:b435 [edited]
<http://www.bmj.com/cgi/content/full/338/may21_2/b435>

"Prevalence of variant CJD in the UK

The number of cases of variant Creutzfeldt-Jakob disease (vCJD) in the United Kingdom has decreased since 2000, but controversy remains about how many people carry the infectious agent and will eventually develop disease. Clewley and colleagues in a limited study add to the debate by assessing 63 007 pairs of tonsils for the only available marker of prion disease, the pathological, partially protease resistant, prion protein. Although more than half of the samples came from people born between 1961 and 1995, when the risk of exposure to bovine spongiform encephalopathy (BSE) infection was high, no convincingly positive tonsil specimens were detected. This study estimated that the prevalence of vCJD in the British population is zero, but with a large confidence interval of 0 to 113 per million.

This result agrees with one UK survey of 2000 tonsil specimens, but it differs from another survey of 1427 tonsils and 11 247 appendices, which found that more than 10 000 people might be incubating the disease. However, despite the discrepancy, the 95 percent confidence intervals of the 2 studies overlap, indicating that the results do not differ significantly and that many people in the UK may be carriers.

The chance that no one in the UK is incubating the disease, as suggested by the lower confidence limit of Clewley and colleagues' study, is unlikely because backup calculations predict up to 100 new cases of vCJD in the next 50 years. This prediction seems reasonable unless most cases of vCJD were missed by surveillance in the past years.

Until December 2008, all 210 people reported to have vCJD (164 in the UK, 46 in other countries) were homozygous for methionine at the polymorphic codon 129 of the prion protein gene (PRNP), suggesting that genetic factors strongly influence the development of disease. Whether people who are heterozygous for methionine and valine or homozygous for valine at this codon (about 60 percent of the population) will develop vCJD in the future is still unknown. However, data *from gene* targeted transgenic mice indicate that these people are also susceptible to BSE and vCJD, although incubation periods are longer than in those who are homozygous for methionine."

Interested readers should consult the original article for further information and references. - Mod.CP]

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[7] Prion evolution & a new reagent
Date: 1 Jan 2010
Source: BBC Health News [edited]
<http://news.bbc.co.uk/1/hi/health/8435320.stm>

Abnormal prion proteins cause at least 20 fatal diseases. Scientists have shown for the 1st time that "lifeless" prion proteins, devoid of all genetic material, can evolve just like higher forms of life. The Scripps Research Institute in the US says the prions can change to suit their environment and go on to develop drug resistance.

Prions are associated with 20 different brain diseases in humans and animals. The scientists say their work suggests new approaches might be necessary to develop therapies for these diseases. In the study, published in the journal Science [see below], the scientists transferred prion populations from brain cells to other cells in culture and observed the prions that adapted to the new cellular environment out-competed their brain-adapted counterparts. When returned to the brain cells, the brain-adapted prions again took over the population.

Charles Weissmann, head of Scripps Florida's department of infectology who led the study, said: "On the face of it, you have exactly the same process of mutation and adaptive change in prions as you see in viruses. This is a timely reminder that prion concerns are not going away and that controls to stop abnormal prions being transmitted to humans through the food system or through blood transfusions must be vigorously maintained."

Professor John Collinge, Medical Research Council Prion Unit stated that: "This means that this pattern of Darwinian evolution appears to be universally active. In viruses, mutation is linked to changes in nucleic acid sequence that leads to resistance. Now, this adaptability has moved one level down -- to prions and protein folding -- and it's clear that you do not need nucleic acid (DNA or RNA) for the process of evolution."

Mammalian cells normally produce cellular prion protein or PrPC. During infections, such as the human form of mad cow disease, known as vCJD, abnormal or mis-folded proteins convert the normal host prion protein into its toxic form by changing its conformation or shape. "It was generally thought that once cellular prion protein was converted into the abnormal form, there was no further change," Prof. Weissmann said. "But there have been hints that something was happening. When you transmit prions from sheep to mice, they become more virulent over time. Now we know that the abnormal prions replicate and create variants, perhaps at a low level initially. But once they are transferred to a new host, natural selection will eventually choose the more virulent and aggressive variants."

Professor John Collinge, of the Medical Research Council's (MRC) Prion Unit, described the research as exciting confirmation of a hypothesis that he had proposed 2 years ago, that there could be a "cloud" or whole array of prion proteins in the body. He called it the cloud hypothesis: "The prion protein is not a clone, it is a quasi-species that can create different protein strains even in the same animal. The abnormal prion proteins multiply by converting normal prion proteins. The implication of Charles Weissmann's work is that it would be better to cut off that supply of normal prion proteins rather than risk the abnormal prion adapting to a drug and evolving into a new more virulent form. You would do this by trying to block the sites on the normal prion protein that the abnormal form locks on to to do its conversion. We know there is an antibody that can do this in mice, and the Medical Research Council's Prion Unit have managed to engineer a human antibody to do this. It is currently undergoing safety tests, and we hope to move to clinical trials by the end of 2011."

Professor Collinge said the MRC was also trying to find more conventional chemical compounds to do this and has been collaborating

with the chemical company GlaxoSmithKline (GSK). He said: "They have given us access to their chemical libraries, which contain millions of compounds, and we have already identified some that may work well. This is a timely reminder that prion concerns are not going away and that controls to stop abnormal prions being transmitted to humans through the food system or through blood transfusions must be vigorously maintained."

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[The abstract and the reference for the Science paper descried above are the following: Science DOI: 10.1126/science.1183218, Published Online 31 Dec 2009.
<http://www.sciencemag.org/cgi/content/abstract/science.1183218>.
Darwinian Evolution of Prions in Cell Culture. By Jiali Li, Shawn Browning, Sukhvir P. Mahal, Anja M. Oelschlegel, Charles Weissmann
At: Department of Infectology, Scripps Florida, 130 Scripps Way, Jupiter, FL 33458, USA.

Abstract: "Prions are infectious proteins consisting mainly of PrPSc, a sheet-rich conformer of the normal host protein PrPC, and occur in different strains. Strain identity is thought to be encoded by PrPSc conformation. We found that biologically cloned prion populations gradually became heterogeneous by accumulating "mutants," and selective pressures resulted in the emergence of different mutants as major constituents of the evolving population. Thus, when transferred from brain to cultured cells, "cell-adapted" prions out competed their "brain-adapted" counterparts, and the opposite occurred when prions were returned from cells to brain. Similarly, the inhibitor swainsonine selected for a resistant substrain, whereas in its absence, the susceptible substrain outgrew its resistant counterpart. Prions, albeit devoid of a nucleic acid genome, are thus subject to mutation and selective amplification."

From a theoretical standpoint, this work has great significance. Nonetheless, the immediate interest of the BBC News report is the information that Professor John Collinge's MRC group has succeeded in engineering a humanised monoclonal antibody that interacts with the sites on the normal prion protein that the abnormal form locks onto to achieve its conversion and that it is hoped eventually to move to clinical trials of this reagent. - Mod.CP]

[see also:
2009

Prion disease update 2009 (10) 20091103.3784
vCJD - Italy: susp. 20091024.3671
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