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	機構処理欄
				2007. 4. 19	該当なし	

一般的名称	人赤血球濃厚液	研究報告の公表状況	Hamaguchi T, Noguchi-Shinohara M, Nakamura Y, Sato T, Kitamoto T, Mizusawa H, Yamada M. Emerg Infect Dis. 2007 Jan;13(1):162-4.	公表国
販売名(企業名)	赤血球M・A・P「日赤」(日本赤十字社) 照射赤血球M・A・P「日赤」(日本赤十字社) 赤血球濃厚液-LR「日赤」(日本赤十字社) 照射赤血球濃厚液-LR「日赤」(日本赤十字社)			日本

研究報告の概要

○日本のプリオン疾患における眼科手術
孤発性クロイツフェルト・ヤコブ病患者のうち10%～20%は、疾患の早期の段階で視覚障害を発症する。一部の患者は、プリオン疾患あるいは加齢による視覚障害のために眼科を受診する。手術後長期間経ってからプリオン疾患を発症した場合、眼科手術による感染性プリオンタンパクの二次感染予防は困難である。日本のプリオン疾患患者597名のうち11名(1.8%)が、発症の前後1ヶ月以内に眼科手術を受けた。眼科医はいずれもプリオンタンパクの感染性を除去するには不十分な滅菌しか行われていない手術器具を再使用していた。眼科医は、プリオン疾患が眼症状を引き起こす可能性があることを認識し、可能な限り使い捨て器具を使用すべきである。

報告企業の意見	今後の対応
日本のプリオン疾患患者597名のうち11名が、発症の前後1ヶ月以内に眼科手術を受け、眼科医はプリオンタンパク質の感染性を除去するには不十分な滅菌しか行われていない手術器具を再使用していたとの報告である。	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。

使用上の注意記載状況・その他参考事項等

赤血球M・A・P「日赤」
照射赤血球M・A・P「日赤」
赤血球濃厚液-LR「日赤」
照射赤血球濃厚液-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

Ophthalmic Surgery in Prion Diseases

Tsuyoshi Hamaguchi,*[1] Moeko Noguchi-Shinohara,* Yosikazu Nakamura,†[2] Takeshi Sato,‡[2] Tetsuyuki Kitamoto,§[2] Hidehiro Mizusawa,¶[2] and Masahito Yamada*[2]

Eleven (1.8%) of 597 patients underwent ophthalmic surgery within 1 month before the onset of prion disease or after the onset. All ophthalmologists reused surgical instruments that had been incompletely sterilized to eliminate infectious prion protein. Ophthalmologists should be aware of prion diseases as a possible cause of visual symptoms and use disposable instruments whenever possible.

Visual impairment occurs in 10% to 20% of patients with sporadic Creutzfeldt-Jakob disease (sCJD) during an early stage of the disease (Heidenhain variant) (*1*,*2*). Some patients with prion diseases may visit ophthalmologists with visual impairment due to prion diseases or with coexisting age-related eye diseases (*3*,*4*).

Infectious prion protein (PrP^{Sc}) was identified in the retina and optic nerve in patients with variant CJD (vCJD) and sCJD (*5*,*6*), and CJD has been transmitted by corneal transplantation (*7*,*8*). In the World Health Organization (WHO) guidelines, eyes were classified as highly infectious tissues (*9*).

Secondary transmission of PrP^{Sc} through ophthalmic surgery could possibly be prevented around the onset of prion diseases, although surgery that is performed long before the onset of prion diseases would not have that potential. It is important to understand the current status of ophthalmic surgery for patients with prion diseases and to clarify the clinical features of the patients with prion diseases who undergo ophthalmic surgery. Here, we describe the relevant data from CJD surveillance in Japan.

The Study

We analyzed the patients with prion diseases who had been registered by the CJD Surveillance Committee in Japan from April 1999 through March 2005. We prospectively investigated each patient with a surveillance protocol that assembled information about life history, previous medical history, clinical history, laboratory data, and results of molecular genetic and pathologic analyses. Written consent, approved by the Institutional Ethics Committee, was obtained from all the patients' families; members of the Surveillance Committee examined the patients and collected the data.

We classified the patients into 4 categories: sCJD, infectious prion diseases, inherited prion diseases, and unclassified prion diseases. sCJD was diagnosed according to the classical criteria established by Masters et al. (*10*). Infectious prion diseases included CJD associated with cadaveric dura mater graft (dCJD) or other iatrogenic opportunities for prion infection, in which the criteria for sCJD were applied for the diagnosis, and vCJD, in which the diagnosis was based on WHO criteria (2001) (*11*). Regarding the accuracy of the diagnosis of inherited prion diseases, cases verified by pathology report were defined as definite, and cases with mutations in the prion protein gene and neuropsychiatric manifestations compatible with prion diseases were defined as probable.

Among patients with a history of ophthalmic surgery, we directed special attention to the patients who had a history of eye surgery within 1 month before the obvious onset of prion disease or after the onset. Because the onset of prion diseases often overlaps with various kinds of prodromal symptoms, determining the precise time point of onset is difficult; therefore, we included the period of 1 month before the obvious onset. To gather information about the ophthalmic surgery, we mailed questionnaires to the ophthalmologists who operated on these patients, requesting the following information: diagnosis of ophthalmologic diseases, surgical procedures performed, changes in the symptoms after the surgery, whether the instruments were reused, and methods of cleaning reused instruments.

To ascertain the clinical features of prion diseases, we analyzed the patient's age at onset and duration of disease course, which was calculated as the interval between the onset and the appearance of the akinetic mutism state or death in the patients who died without akinetic mutism. Among early clinical manifestations of prion diseases, dementia and visual disturbance are major determinants that would influence the indication for ophthalmic surgery, so we grouped the patients according to whether they had dementia or visual impairment within 2 months after onset of symptoms.

The sex distribution of the patients who had ophthalmic surgery around the time of onset of clinical symp-

*Kanazawa University Graduate School of Medical Science, Kanazawa, Japan; †Jichi Medical University, Shimotsuke, Japan ‡National Center for Neurology and Psychiatry, Ichikawa, Japan; §Tohoku University Graduate School of Medicine, Sendai, Japan; and ¶Tokyo Medical and Dental University, Tokyo, Japan

[1]Current affiliation: Ishikawa Prefecture Central Hospital, Kanazawa, Japan

[2]Member, Creutzfeldt-Jakob Disease Surveillance Committee, Japan

toms and those who did not was compared by Fisher exact tests, and differences in age at onset and disease duration were compared by Mann-Whitney U tests. We used χ^2 tests to compare the distribution of the patients with or without dementia or visual impairment within 2 months of onset. Statistical significance was defined as $p<0.05$.

We found 597 patients with definite or probable diagnosis of prion diseases: 468 (78.4%) with sCJD; 78 (13.1%) with inherited prion diseases; 48 (8.0%) with infectious prion diseases, including 47 cases of dCJD; and 1 patient with vCJD and 3 patients with unclassified CJD.

Thirty-seven patients (6.2%) had a history of ophthalmic surgery at some time in their lives. Among them, 11 patients (1.8%) underwent ophthalmic surgery within 1 month before the obvious onset of prion disease or after the onset. Except for 1 patient with Gerstmann-Sträussler-Scheinker disease, all of these patients had sCJD. There have been no reports of the development of prion diseases in patients who underwent ophthalmic surgery after the ophthalmic surgery of patients with prion diseases.

Ten patients with sCJD underwent ophthalmic surgery within 14 months of symptom onset, and 8 of them had ophthalmic surgery within 4 months of symptom onset (Table 1). At clinical onset, 4 patients exhibited visual symptoms, 5 had dementia, and 1 patient had a gait disturbance. All patients underwent surgery for cataracts, except for 1 patient who underwent surgery for a detached retina. According to the reports on the surgical outcome by the ophthalmologists of 7 patients, visual disturbance was unchanged in 2 patients, deteriorated in 1, and improved to some extent in 4 after surgery. All ophthalmologists reused some surgical instruments and cleaned instruments by either autoclaving or the ethylene oxide gas method, which have been reported to incompletely sterilize PrP^{Sc} (*9,12*).

Clinical features were compared between sCJD patients who did and did not have ophthalmic surgery (Table 2). The patients who had ophthalmic surgery had a significantly longer disease duration than those without ($p=0.0004$). Regarding early clinical symptoms within 2 months after onset, the subgroup with visual symptoms without dementia was significantly overrepresented among the patients who had ophthalmic surgery compared with those who did not have surgery ($p= 0.0004$).

Conclusions

Our study showed that, in 1.8% of the patients with prion diseases, eye tissues were operated on within 1 month before the obvious onset of prion disease or after the onset. In addition, the sCJD patients who underwent surgery had a significantly longer duration of the disease course as well as significant overrepresentation of visual symptoms without dementia in the early phase, compared with patients who did not have ophthalmic surgery.

The prevalence of ophthalmic surgery around the time of clinical onset of prion diseases in our study is similar to that (2.0%) in a report from the United Kingdom (*13*). In the UK study (*13*), patients with Heidenhain variant cases constituted 40% of sCJD patients who had ophthalmic surgery. Early visual impairment (due to prion diseases) would prompt ophthalmologists to perform surgery.

Currently, cataract surgery is recommended to improve physical or cognitive function in elderly patients (*14,15*). It should be noted that, after performing eye surgery on patients with prion disease, all ophthalmologists reused surgical instruments that were sterilized with procedures that are incomplete for the sterilization of PrP^{Sc}, although the WHO infection control guidelines for prion diseases (*9*) strongly recommend single-use surgical

Table 1. Characteristics of sCJD patients and ophthalmic surgery*

Patient no.	Sex/age, y†	Disease duration, mo‡	Symptom at sCJD onset	Ophthalmic disease	Interval, mo§	Visual symptoms after surgery	Reused instruments	Cleaning method
1	M/81	8	Visual	Cataract	4	NA	NA	NA
2	M/61	15	Dementia	Cataract	0	Improved	Yes	Autoclave (135°C for 9 min)
3	F/64	20	Visual	Cataract	14	Not changed	Yes	EOG
4	F/59	3	Dementia	Detached retina	−1	Improved	Yes	EOG
5	F/57	10	Dementia	Cataract	10	NA	NA	NA
6	F/79	5	Dementia	Cataract	−1	Improved	Yes	EOG
7	M/74	16	Visual	Cataract	3	Improved	Yes	Autoclave (132°C for 10 min), EOG
8	F/63	5	Visual	Cataract	1	Deteriorated	Yes	Autoclave (132°C for 10 min)
9	M/79	6	Gait disturbance	Cataract	2	Not changed	Yes	Autoclave (121°C for 60 min)
10	F/66	3	Dementia	Cataract	1	NA	NA	NA

*sCJD, sporadic Creutzfeldt-Jakob disease; visual, visual impairment; NA, not available; EOG, ethylene oxide gas.
†At sCJD onset.
‡Disease duration, the duration from onset to akinetic mutism state or death if the patients never displayed akinetic mutism.
§Between surgery and sCJD symptoms.

Table 2. Clinical symptoms of sCJD within 2 mo after disease onset*

Characteristic	Ophthalmic surgery		Total	p value
	No, n = 458	Yes, n = 10		
Female/male	263/195	6/4	269/199	0.57
Age at onset, y; mean ± SD	66.8 ± 9.9	68.3 ± 9.1	66.8 ± 9.9	0.74
Disease duration,† mean ± SD	4.2 ± 4.8	9.1 ± 6.0	4.3 ± 4.9	0.0004
Clinical symptoms (%)				
Dementia (+)/visual impairment (+)	153 (34.2)	4 (40.0)	157 (34.3)	
Dementia (+)/visual impairment (–)	239 (53.3)	3 (30.0)	242 (52.8)	0.0004
Dementia (–)/visual impairment (+)	16 (3.6)	3 (30.0)	19 (4.1)	
Dementia (–)/visual impairment (–)	40 (8.9)	0	40 (8.7)	

*sCJD, sporadic Creutzfeldt-Jakob disease; SD, standard deviation; +, with; –, without.
†Disease duration, the duration from onset to akinetic mutism or death if patients never displayed akinetic mutism.

instruments for procedures involving highly infective tissues. The fact that no secondary iatrogenic cases that could be attributed to surgical procedures were found during our investigation does not diminish the need for ophthalmologists to be aware of CJD as a cause of visual symptoms (including symptoms mimicking those of cataracts) and highlight the importance of using disposable instruments whenever possible to avoid cross-contamination.

Acknowledgments

We thank Fumio Moriwaka, Yoshiyuki Kuroiwa, Masatoyo Nishizawa, Nobuyuki Sodeyama, Masatoshi Takeda, Yusei Shiga, Shigetoshi Kuroda, Shigeki Kuzuhara, Jun Tateishi, Hiroyuki Murai, and Shigeo Murayama for the CJD surveillance.

The CJD Surveillance Committee belongs to the Research Group on Prion Disease and Slow Virus Infection, funded by the Ministry of Health, Labour and Welfare, Japan; the funding source had no involvement in the publication of this article.

Dr Hamaguchi is a clinical research fellow in the Department of Neurology and Neurobiology of Aging, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan. His primary research interest is prion diseases.

References

1. Kropp S, Schulz-Schaeffer WJ, Finkenstaedt M, Riedemann C, Windl O, Steinhoff BJ, et al. The Heidenhain variant of Creutzfeldt-Jakob disease. Arch Neurol. 1999;56:55–61.
2. Lueck CJ, McIlwain GG, Zeidler M. Creutzfeldt-Jakob disease and the eye. II. Ophthalmic and neuro-ophthalmic features. Eye. 2000;14:291–300.
3. Cooper SA, Murray KL, Heath CA, Will RG, Knight RSG. Isolated visual symptoms at onset in sporadic Creutzfeldt-Jakob disease: the clinical phenotype of the "Heidenhain variant." Br J Ophthalmol. 2005;89:1341–2.
4. Tullo A. Creutzfeldt-Jakob disease and eye surgery—new disease, old disease. J Cataract Refract Surg. 2003;29:629–31.
5. Head MW, Northcott V, Rennison K, Ritchie D, McCardle L, Bunn TJ, et al. Prion protein accumulation in eyes of patients with sporadic and variant Creutzfeldt-Jakob disease. Invest Ophthalmol Vis Sci. 2003;44:342–6.
6. Head MW, Peden AH, Yull HM, Ritchie DL, Bonshek RE, Tullo AB, et al. Abnormal prion protein in the retina of the most commonly occurring subtype of sporadic Creutzfeldt-Jakob disease. Br J Ophthalmol. 2005;89:1131–3.
7. Duffy P, Wolf J, Collins G, DeVoe AG, Streeten B, Cowen D. Possible person-to-person transmission of Creutzfeldt-Jakob disease. N Engl J Med. 1974;290:692–3.
8. Heckmann JG, Lang CJG, Petruch F, Druschky A, Erb C, Brown P, et al. Transmission of Creutzfeldt-Jakob disease via a corneal transplant. J Neurol Neurosurg Psychiatry. 1997;63:388–90.
9. World Health Organization (WHO). WHO infection control guidelines for transmissible spongiform encephalopathies. Report of a WHO consultation, Geneva, Switzerland, 1999 March 23–26. Geneva: WHO; 1999. Available from http://www.who.int/csr/resources/publications/bse/WHO_CDS_CSR_APH_2000_3/en/
10. Masters CL, Harris JO, Gajdusek DC, Gibbs CJ Jr, Bernoulli C, Asher DM. Creutzfeldt-Jakob disease: patterns of worldwide occurrence and the significance of familial and sporadic clustering. Ann Neurol. 1979;5:177–88.
11. World Health Organization (WHO). The revision of the variant Creutzfeldt-Jakob (vCJD) case definition. Report of a WHO consultation. Edinburgh, United Kingdom, 2001 17 May (WHO/CDS/CSR/EPH/2001.5). Geneva: WHO; 2001.
12. Taylor DM. Inactivation of transmissible degenerative encephalopathy agents: a review. Vet J. 2000;159:10–7.
13. S-Juan P, Ward HJ, De Silva R, Knight RS, Will RG. Ophthalmic surgery and Creutzfeldt-Jakob disease. Br J Ophthalmol. 2004;88:446–9.
14. Brenner MH, Curbow B, Javitt JC, Legro MW, Sommer A. Vision change and quality of life in the elderly. Response to cataract surgery and treatment of other chronic ocular conditions. Arch Ophthalmol. 1993;111:680–5.
15. Tamura H, Tsukamoto H, Mukai S, Kato T, Minamoto A, Ohno Y, et al. Improvement in cognitive impairment after cataract surgery in elderly patients. J Cataract Refract Surg. 2004;30:598–602.

Address for correspondence: Masahito Yamada, Department of Neurology and Neurobiology of Aging, Kanazawa University Graduate School of Medical Science, 13-1, Takara-machi, Kanazawa 920-8640, Japan; email: m-yamada@med.kanazawa-u.ac.jp

別紙様式第2-1

No. 12

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	機構処理欄
				2007. 5. 22	該当なし	
一般的名称	白血球除去人赤血球浮遊液		研究報告の公表状況	ABC Newsletter. 2007 May 4.	公表国 米国	
販売名(企業名)	白血球除去赤血球「日赤」(日本赤十字社) 照射白血球除去赤血球「日赤」(日本赤十字社)					

研究報告の概要

○イスラエルはvCJD及び肝炎に関する供血延期基準を変更

イスラエルで血液事業を行っている赤盾ダビデ社(Magen David Adom:MDA)は、変異型クロイツフェルト・ヤコブ病(vCJD)に関する供血延期基準を変更し、1980年以降にフランス居住歴がある人の供血を可能とした。イギリスでウシ海綿状脳症(「狂牛病」)の流行が始まった1980年から10年間のうちにイギリス、アイルランド、ポルトガルに居住歴のある人は、引き続き供血延期となる。vCJDの発生リスクはイギリスで600/100万、アイルランドで17/100万、ポルトガルで20/100万であるのに対し、フランスではわずかに1.7/100万であり、リスク要因としてはあまりにも小さい。このため、MDAは(保健省の承認を得て)フランス系移民及び旅行者に対し制限を緩和することを決定した。

加えてMDAは、輸血を受けた人、B型肝炎やC型肝炎患者と一緒に住んでいた人、入れ墨を入れた人、胃や小腸の生検を含む内視鏡検査を受けた人の供血延期期間を1年から6ヵ月に短縮した(内視鏡検査を受けた人の供血延期は、生検に使用された内視鏡が完全に滅菌されずに再使用された場合、ウイルス感染症やvCJDを伝播しうるとの理論的可能性による)。

また、動物に噛まれた人は、噛んだ動物が不明であったり検査を受けていない場合、これまでの12ヵ月後ではなく2ヵ月後から供血が可能となる。

使用上の注意記載状況・その他参考事項等

白血球除去赤血球「日赤」
照射白血球除去赤血球「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

報告企業の意見	今後の対応
イスラエルで血液事業を行っている赤盾ダビデ社は変異型クロイツフェルト・ヤコブ病に関する供血延期基準を変更し、1980年以降フランスに居住歴がある人の供血を可能にしたとの報告である。	日本赤十字社は、輸血感染症防止のため輸血歴のあるドナーを無期限に献血延期としている。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日より英国滞在歴1日以上の方からの献血を制限している。さらに、血液製剤の保存前白血球除去を導入し、平成19年1月16日には全ての輸血用血液への保存前白血球除去の導入が完了した。今後もCJD等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。

On the Difference between What People Say and What They Do About Risk

"If you ask me based on findings, (if people are) afraid of food recalls, the answer is no. So people aren't really concerned or scared, but the funny thing is that sales are still down."

– Dr. Sylvain Charlebois, of the University of Regina, on a study he helped conduct of the Canadian food safety system. The study sought to understand the consumer's perception of food recalls. According to Dr. Charlebois, people are loath to admit they are scared, and the numbers bear that out. Canadian Leader-Post, 4/12/07

Strike at Southern California Red Cross (continued from page 5)

The job action was not expected to threaten the local blood supply. Southern California already imports about 40 percent, and Red Cross officials said it was possible more might be shipped in as a result of the walkout.

Both Red Cross and union officials called for the public to continue donating blood. The union distributed lists of local hospitals where people could give blood, and the Red Cross directed people to the national Red Cross blood donation Web site, www.givelife.org (Sources: Associated Press, 4/30/07; *Los Angeles Times*, 5/3/07) ♦

Israel Changes Blood Donor Deferral Criteria for vCJD, Hepatitis

Israel's national blood service Magen David Adom (MDA) has changed its variant Creutzfeldt-Jakob disease (vCJD) donor deferral criteria to allow anyone who lived in France from 1980 to become a blood donor in Israel. Those who lived in England, Ireland and Portugal for a decade after 1980, when England's bovine spongiform encephalopathy ("mad cow") epidemic began, are still barred from donating blood in Israel and Europe.

MDA blood services director Eilat Shinar, MD told *The Jerusalem Post* last month (4/16/07) that the prevalence of vCJD is around 600 per million in England and between 17 and 20 per million in Ireland and Portugal, but only 1.7 per million in France and thus too small to be a risk factor. For this reason, the European authorities and subsequently MDA (with Health Ministry approval) decided to liberalize the policy for French immigrants and tourists, Dr. Shinar said.

In addition, MDA shortened the deferral period from one year to six months for people who received a blood transfusion, lived with a patient who had hepatitis B or C, had a tattoo done or underwent an endoscopic examination including a biopsy of the stomach or small intestine. (Deferral for endoscopic examinations is based on the fact that the reuse of endoscopes used for biopsy theoretically can transmit viral infections or vCJD if not thoroughly sterilized).

Finally, anyone who was bitten by an unidentified and untested animal now can donate blood in Israel two months after the bite instead of the previous 12 month deferral. ♦