別紙様式第２－１

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 平成 19 年 5 月 7 日	新医薬品等の区分 該当なし	機構処理欄
一般的名称	ﾃｸﾈﾁｳﾑ大凝集人血清ｱﾙﾌﾞﾐﾝ（99mTc）		研究報告の公表状況	ProMED-mail／20070423.1325(2007 年 4 月 23 日) 1:Herald Sun online、2: Mailman School of Public Health, Columbia University, press release	公表国 オーストラリア	
販売名（企業名）	テクネ MAA キット（富士フイルムＲＩファーマ株式会社）					

研究報告の概要	使用上の注意記載状況・その他参考事項等
オーストラリア（ヴィクトリア）において、一人のドナーから臓器提供を受けた 3 人（腎臓を移植された 63 歳女性、肝臓を移植された 64 歳の男性、腎臓を移植された 3 例目）の死因について、コロンビア大学とメルボルンの科学者らによって新たなウイルス（リンパ球性脈絡髄炎ウイルスに関連するアレナウイルス科）が発見された。しかしこのウイルスが単に付着しているだけか、組織拒絶と死の原因となるかどうかは未解決である。	特になし

報告企業の意見	今後の対応
臓器移植後死亡した 3 例の死因についての研究報告であり、これまで知られていない新ウイルス（リンパ球性脈絡髄炎ウイルスに関連するアレナウイルス科）が発見され、同科には出血熱性のラッサウイルスやマチュポウイルス等あることより、重大な感染症である可能性が考えられる。 本報告は、新たに判明した感染症に関するものであり、かつ、重大な感染症に関するものと判断する。	本報告はヒト血液を原料とする血漿分画製剤等とは直接関連するものではなく、現時点で特に当該生物由来製品に関し、措置等を行う必要はないと判断する。しかしこのウイルスが単に臓器に付着しているだけか、組織拒絶と死の原因となるかどうかは未解決であると報告されているため、今後も情報収集が必要であると考える。

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Archive Number 20070423.1325
Published Date 23-APR-2007
Subject PRO/AH/EDR> Arenavirus, organ transplants - Australia (VIC)

ARENAVIRUS, ORGAN TRANSPLANTS - AUSTRALIA (VICTORIA)
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A ProMED-mail post
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[1]
Date: Sun 22 Apr 2007
Source: Herald Sun online [edited]
<http://www.news.com.au/sundayheraldsun/story/0,,21598166-2862,00.html

Australia: Novel virus responsible for deaths of organ donation recipi
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A virus unknown to medical science was behind the deaths of 3 Victorians who received organs from the one donor. The unnamed bug has been linked to Ebola virus, [a virus] responsible for the deaths of thousands in central Africa since the 1970s. [This is an incorrect statement. The organ transplant-associated virus is not related to Ebola virus; see part [2] below. - Mod.CP]. After baffling local scientists, experts from New York's Columbia University were called in to help solve the mystery of the multiple transplant deaths being investigated by the coroner.

Initial investigations and tests had been unable to determine any common link between the donor and the 3 recipients. The presence of the virus in the recipients is thought to be a world first. One of the New York team said: "The discovery of this virus is of national and international significance."

The Sunday Herald Sun revealed the deaths in February 2007. A 63-year-old woman died after receiving a kidney transplant at Austin Hospital. A 64-year-old man died after receiving a liver transplant there. The 3rd victim received a kidney at Royal Melbourne Hospital.

The male donor whose organs carried the suspected killer bug had died in Dandenong Hospital of a brain hemorrhage in December 2006 after returning from overseas; it is believed most of his trip was spent in Europe.

The virus is part of the rodent-borne arenavirus family and can cause "old-world" diseases such as Yellow Fever, Ebola and Lymphocytic choriomeningitis. [This statement is incorrect: yellow fever is caused by a flavivirus and Ebola hemorrhagic fever is caused by a filovirus; only lymphocytic choriomeningitis (LCM) is caused by an old-world arenavirus. - Mod.CP]. Victoria's acting Chief Health Officer, Dr John Carnie, confirmed the virus [LCM virus?] had been detected in multiple samples from all 3 transplant patients. But there was no evidence the virus represented a public health risk, he said.

Health authorities are examining whether future donated organs can be screened for [LCM?] virus. A spokesman for the Victoria Coroner's office said families of the victims were told yesterday [21 Apr 2007]. There would be a formal inquest.

Experts from Columbia's Greene Infectious Diseases Laboratory helped

solve the mystery. Initial investigations and tests were unable to determine any common link between the donor and the 3 recipients. Dr Carnie said the risk to the public was minimal because "these viruses [?] affect immunocompromised people, and it is rarely fatal in those with normal immune systems. We have not had any indication of any unexplained illnesses among families of the donor or recipients," he said. "This would be the case if it was transmissible person to person. Our supposition is it was transmitted by organ transplantation."

Cutting edge techniques were used for the 1st time by the Greene lab -- in collaboration with Victorian Infectious Diseases Reference Laboratory -- to gene sequence the virus. "Our gene technology enables unbiased sequencing of all agents present," Columbia's Prof. Ian Lipkin said. "We found a handful (of combinations) that were related to Lassa virus or LCM virus [both old world arenaviruses - Mod.CP]. Using these clues we can confidently say this is a new virus, present in the original organs and so different than anything seen before."

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Communicated by:
ProMED-mail Rapporteur Brent Barrett

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[2]
Date: Sat 21 Apr 2007
Source: Mailman School of Public Health, Columbia University, press release [edited]
<http://www.prnewswire.com/cgi-bin/stories.pl?ACCT=104&STORY=/www/stor

Scientists Discover New Virus Responsible for Deaths of 3 Transplant Recipients From Single Donor in Victoria, Australia
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Knowledge of genetic sequence of virus will enable improvements in screening to enhance transplantation safety. Scientists in the Greene Infectious Disease Laboratory of Columbia University Mailman School of Public Health and colleagues in the Victoria Infectious Diseases Reference Laboratory in Melbourne, Australia and 454 Life Sciences have discovered a new virus that was responsible for the deaths of 3 transplant recipients who received organs from a single donor in Victoria, Australia.

The previously unknown virus, which is related to lymphocytic choriomeningitis virus (LCMV), was found using rapid sequencing technology established by 454 Life Sciences and bioinformatics algorithms developed in the Greene Laboratory with support from the National Institute of Allergy and Infectious Diseases. Known strains of LCMV have been implicated in a small number of cases of disease transmission by organ transplantation [see references below], however, the newly discovered virus is sufficiently different that it could not be detected using existing screening methods.

Over 30 000 organ transplants are performed in the U.S. each year. Knowledge of the genetic sequence of this virus will enable improvements in screening that will enhance the safety of transplantation.

Ian Lipkin, MD, director of the Greene Laboratory and Principal Investigator of the Northeast Biodefense Center, emphasized the importance of academic, public health, and industrial partnership in this work. "This was a team effort. Drs. Mike Catton and Julian Druce at the Victorian Infectious Disease Reference Laboratory reached out to us after a comprehensive state-of-the-art investigation failed to turn up leads," stated Dr. Lipkin. "We succeeded in identifying the virus responsible for the deaths by building on their work and utilizing new tools for pathogen surveillance and discovery developed in the Greene Laboratory and 454 Life Sciences."

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Communicated by: ProMED-mail <promed@promedmail.org>

[Lymphocytic choriomeningitis virtu (LCMV) is the type species of the genus _Arenavirus_ of the _Areanviridae_ family of bipartitie genome

RNA viruses. The reservoir hosts of almost all arenaviruses are rodents. LCMV is found in wild and laboratory mice, and other related "old world" arenaviruses are found in African species of rodents. Human LCMV infection may occur in rural and urban areas with high densities of rodents. Laboratory-acquired infections occur sporadically, and, previously, there have been a small number of cases of LCMV transmission by organ transplantation as mentioned by Professor Lipkin above. The virus detected by Professor Lipkin's group appears to be an LCMV-like agent but distinct from previously isolated strains of LCMV. It is unresolved, however, whether these organ-transplanted viruses are merely passengers or are responsible also for tissue-rejection illness and death. - Mod.CP]

[see also:
2005

LCMV, transplant recipients, fatal - USA (02) 20050526.1459
LCMV, transplant recipients, fatal - USA 20050524.1426
1995

LCMV & birth defects - USA 19951119.1095]
.....mpp/cp/msp/lm

別紙様式第2-1

No. 10

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	AbuBakar S, Sam IC, Wong PF, MatRahim N, Hooi PS, Roslan N. Emerg Infect Dis. 2007 Jan;13(1):147-9.	公表国 マレーシア
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)			

研究報告の概要

○マレーシアにおけるチクングニヤウイルス感染の再興
最近マレーシアでは、7年間検出されていなかったチクングニヤウイルス感染が再興した。分離ウイルスのゲノム配列は、1998年のアウトブレイク時のMalaysian 分離ウイルスの配列との相同性が高かった。この感染の再興は、他のインド洋諸国における流行には関与しないが、マレーシア特有のチクングニヤが流行する可能性が浮上している。

報告企業の意見	今後の対応
マレーシアで7年間検出されていなかったチクングニヤウイルス感染が再興し、ウイルスのゲノム配列は他のインド洋諸国における流行株とは異なっていたとの報告である。	日本赤十字社では、輸血感染症対策として問診時に海外渡航歴の有無を確認し、帰国後4週間は献血不適としている。国内でチクングニヤ感染が確認されたため、渡航歴確認の徹底を図っている。また、チクングニヤ熱の既往歴がある場合、治癒後6ヵ月間は献血不適としている。今後も引き続き、新興・再興感染症の発生状況等に関する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

Reemergence of Endemic Chikungunya, Malaysia

Sazaly AbuBakar,* I-Ching Sam,* Pooi-Fong Wong,* NorAziyah MatRahim,* Poh-Sim Hooi,* and Nuruliza Roslan*

Chikungunya virus infection recently reemerged in Malaysia after 7 years of nondetection. Genomic sequences of recovered isolates were highly similar to those of Malaysian isolates from the 1998 outbreak. The reemergence of the infection is not part of the epidemics in other Indian Ocean countries but raises the possibility that chikungunya virus is endemic in Malaysia.

Chikungunya, a mosquitoborne disease first described in Tanzania (formerly Tanganyika) in eastern Africa in 1952, is caused by chikungunya virus (CHIKV), an alphavirus belonging to the *Togaviridae* family. The disease occurs in Africa and various parts of Asia and is endemic in several southeast Asian countries, including Thailand, Indonesia, and the Philippines. Only 1 known outbreak has occurred in Malaysia, in 1998–1999 when ≥51 persons in Port Klang were infected (*1*).

From March through April 2006, an outbreak of CHIKV infection was reported in Bagan Panchor (4°31′N, 100°37′E), an isolated coastal town 50 km west of Ipoh, the state capital of Perak, in northwest Malaysia. At least 200 villagers were infected, with no deaths reported. This was the second known outbreak in Malaysia, 7 years after the previous one. This reemergence coincided with reports of ongoing epidemics of CHIKV infection in India and almost all the island nations of the Indian Ocean, with >200,000 cases in the French island of Reunion alone since February 2005 (*2*).

Why and how the recent infection reappeared in Malaysia remains unknown. The apparent absence of CHIKV for 7 years may be due to failure to detect low-level, continued transmission in humans, particularly because the symptoms may be mistaken for dengue fever. Alternatively, this outbreak could have originated from a viremic traveler from an endemic country (such as neighboring Thailand or Indonesia), but proximity of Malaysia to the Indian Ocean raises the possibility of an extension of the epidemic, with Malaysia being the furthest point yet of the expanding epidemic frontline.

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The Study

We received serum samples from 11 patients who had symptoms typical of CHIKV infection (Table). Samples were injected into Vero and C6/36 mosquito cells. Indirect immunofluorescence assays for immunoglobulin M (IgM) and IgG were performed using the patients' sera and CHIKV-infected cells fixed onto glass slides, as previously described (*1*). A CHIKV isolate (SM287) reported previously (*3*) was used to prepare the slides as a positive control for subsequent studies. Serum samples from patients who did not have symptoms of chikungunya, including patients with dengue fever, were used as negative controls. Nucleic acid amplification was performed using RNA extracted directly from the patients' sera or from cell cultures (Table). At least 3 different primer pairs specific for envelope glycoprotein E1 (E1), glycoprotein E2 (E2), and nonstructural protein 1 (nsP1) genes of CHIKV were used (*4,5*). Confirmation of the amplified DNA fragments was done by DNA sequencing. Phylogenetic relationships were examined using the E1, E2, and nsP1 gene sequences of the isolates and all other available CHIKV sequences obtained from GenBank or the previous studies (online Appendix Table, available from www.cdc.gov/ncidod/EID/13/1/147-appT.htm). Sequences were aligned and phylogenetic trees were drawn as previously described (*6*).

CHIKV infection was confirmed in 8 of 11 patients. CHIKV sequences were amplified directly from serum samples from 5 patients in the acute phase of disease. Of these, 4 CHIKV isolates were eventually cultured. IgM and IgG were detected in serum samples from 3 other patients in the convalescent phase (data not shown). In 1 patient, CHIKV sequences were amplified from serum samples obtained as late as 9 days after onset of symptoms (data not shown). The PCR amplification method, thus, could be useful for early detection of CHIKV infection in suspected outbreak situations.

The genomic sequence of the E1, E2, and nsP1 genes in the CHIKV isolates shared high similarity (>90%) to all the known CHIKV except West African CHIKV (≈86% similarity). The sequences were only ≈70% related to o'nyong-nyong virus, the most closely related alphavirus, which is present only in certain parts of Africa. Previous phylogenetic studies showed that CHIKV strains were clustered into 3 distinct groups based on origin from West Africa, Central/East Africa, or Asia (*7–13*). Phylogenetic trees drawn using E1 (Figure), E2, and nsP1 (data not shown) gene sequences clustered the recent Malaysian isolates into a group with other known CHIKV Asian isolates. The cluster, however, was distinctly separated (100% bootstrap support) from the African isolates and all the known isolates of the ongoing CHIKV epidemics of the Indian Ocean islands (*7–9,11,13*). This makes it unlikely that the outbreak in Malaysia is part of the ongoing epidemics,

Table. Identification of virus by PCR amplification and serologic analysis*

Patient		Chikungunya						Dengue fever	
		PCR†			Serology				Serology
Age (y)	Sex	E1	E2	nsP1	IgM	IgG	Culture	PCR‡	IgM
6	M	+	+	+	–	–	+§	–	–
34	M	+	+	+	–	–	+¶	–	–
40	M	+	+	+	–	–	+#	–	–
26	F	+	+	+	–	–	+**	ND	–
62	M	+	+	+	–	–	–††	ND	–
			(day 5 after onset)						
		–	–	–	+	+	ND	ND	ND
			(day 15 after onset)						

*IgM, immunoglobulin M; IgG, immunoglobulin G; +, positive; –, negative; ND, not determined.
†PCR amplifications were performed for detection of envelope glycoprotein E1 (E1), glycoprotein E2 (E2), and nonstructural protein 1 (nsP1) genes of chikungunya virus.
‡Multiplex PCR amplifications were performed for detection of dengue virus type 1–4.
§Isolate MY/0306/BP37348.
¶Isolate MY/0306/BP37350.
#Isolate MY/0306/BP37352.
**Isolate MY/0406/BP37437.
††Isolate MY/0306/BP34198.

despite its proximity to the region and timing of the outbreak. The phylogenetic tree, on the other hand, suggests that the isolates from the current Malaysia outbreak share a common ancestral lineage to the 2 Malaysian isolates recovered in 1998 (*4*; GenBank accession nos. AF394210 and AF394211) but have a slight genetic distance from all other Asian isolates.

Conclusions

On the basis of all available sequences of isolates from the neighboring countries where CHIKV is endemic, Thailand and Indonesia, the outbreak in Malaysia likely did not originate from either of these countries, which means the outbreak could have originated from an endemic CHIKV cycle not previously identified in Malaysia. A serologic survey of human serum samples collected during 1965–1969 in west Malaysia showed neutralizing antibodies to CHIKV among adults, especially those inhabiting the rural northern and eastern states bordering Thailand (*14*). The same authors also reported in an earlier study evidence of CHIKV-neutralizing antibodies in wild monkeys, a pig, and a chicken and suggested that a CHIKV sylvatic transmission cycle involving primates and possibly nonprimates exists in Malaysia. A sylvatic transmission cycle of the virus has been described in Africa and may play a role in the episodic emergence and reemergence of CHIKV infection (*15*). Before 1998, CHIKV had not been isolated from humans or animals in Malaysia, and no clinical disease caused by CHIKV had been reported. However, in the absence of active surveillance since the 1965 study, whether the apparent absence of CHIKV over the years and between the 2 recent outbreaks in Malaysia is due to an unidentified sylvatic transmission cycle or silent transmission among humans cannot be determined. Further investigation is required to examine these possibilities. Understanding this disease in Southeast Asia is critical because CHIKV shares the same mosquito vectors as dengue virus, which is endemic to the region.

Phylogenetic analysis showed that CHIKV from the recent 2006 outbreak in Malaysia is highly similar to isolates from the 1998 outbreak. At the 3 genes examined,

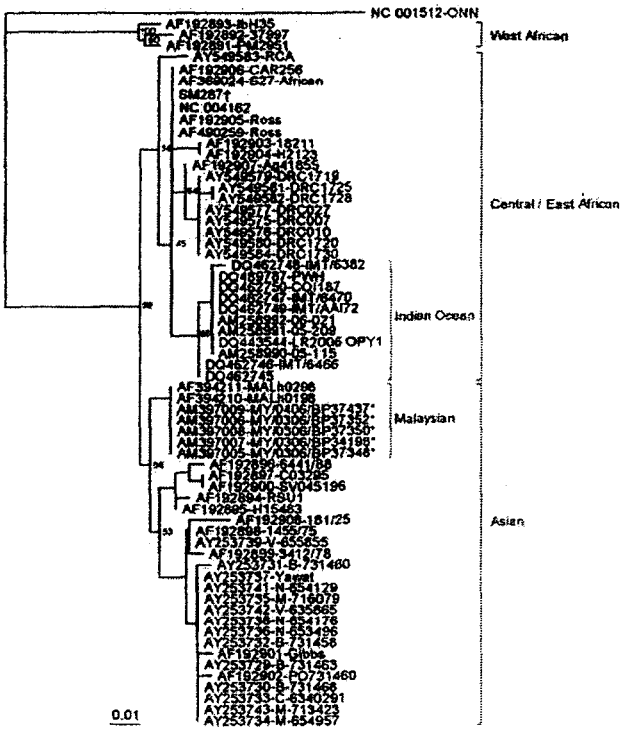

Figure. Phylogenetic relationships of chikungunya virus isolates from the 2006 Malaysia outbreak. The neighbor-joining tree was constructed using nucleic acid sequences of the envelope glycoprotein E1 gene, with o'nyong nyong virus (GenBank accession no. NC_001512) as the outgroup virus. * indicates isolates from the Malaysia 2006 outbreak; † indicates Australia SM287. Bootstrap values are shown as percentages derived from 1,000 samplings. The scale reflects the number of nucleotide substitutions per site along the branches.

the isolates differ from the ongoing Indian Ocean epidemic isolates and known isolates from Thailand and Indonesia. These findings support the possibility that the outbreak originated from an endemic infection in Malaysia.

Acknowledgments

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Dr AbuBakar is professor and head of the Department of Medical Microbiology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia. His research interests include the pathogenesis of emerging virus infections.

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