医薬品　研究報告　調査報告書

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<tr><td>研究報告の概要</td><td colspan="5">問題点：コスタリカにおいて、高病原性で新しい血清型に分類されるレプトスピラ株がヒトから分離された。

コスタリカにおいて、地域で流行しているレプトスピラの血清型を同定するため、通院している患者からレプトスピラを分離・解析した。レプトスピラ症の症状を呈して入院していた患者から分離された MAVJ401 株は、ウサギ抗血清パネルで Javanica 血清群型の血清型に対して著しく凝集価が上昇したが、標準的な Cross Agglutinin Absorption Test では血清学的にユニークであった。そのため MAVJ401 株は、Javanica 血清群型の新しい血清型（Arenal と命名）であると推測された。また、MAVJ401 株は、遺伝子学的解析によりラテンアメリカ諸国で多く発生している種である Leptospira santarosai に分類された。同じ地区の重症患者から分離された株も Arenal と同一の血清型であったことから、これが外来の血清型ではなく、この地域に流行する新規の高病原性の血清型であると考えられた。この新しい血清型に分類されるレプトスピラ株は、地域の公衆衛生と家畜衛生に脅威をもたらすおそれがある。</td><td>使用上の注意記載状況・
その他参考事項等

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<tr><td colspan="3">報告企業の意見</td><td colspan="3">今後の対応</td><td></td></tr>
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別紙

一般的名称	①人血清アルブミン、②人血清アルブミン、③人血清アルブミン*、④人免役グロブリン、⑤乾燥ペプシン処理人免疫グロブリン、⑥乾燥スルホ化人免疫グロブリン、⑦乾燥スルホ化人免疫グロブリン*、⑧乾燥濃縮人活性化プロテインC、⑨乾燥濃縮人血液凝固第Ⅷ因子、⑩乾燥濃縮人血液凝固第Ⅸ因子、⑪乾燥抗破傷風人免疫グロブリン、⑫抗 HBs 人免疫グロブリン、⑬トロンビン、⑭フィブリノゲン加第ⅩⅢ因子、⑮乾燥濃縮人アンチトロンビンⅢ、⑯ヒスタミン加人免疫グロブリン製剤、⑰人血清アルブミン*、⑱人血清アルブミン*、⑲乾燥ペプシン処理人免役グロブリン*、⑳乾燥人血液凝固第Ⅸ因子複合体*、㉑乾燥濃縮人アンチトロンビンⅢ
販売名(企業名)	①献血アルブミン20“化血研”、②献血アルブミン25“化血研”、③人血清アルブミン“化血研”*、④“化血研”ガンマーグロブリン、⑤献血静注グロブリン“化血研”、⑥献血ベニロンーⅠ、⑦ベニロン*、⑧注射用アナクトC2,500単位、⑨コンファクトF、⑩ノバクトM、⑪テタノセーラ、⑫ヘパトセーラ、⑬トロンビン“化血研”、⑭ボルヒール、⑮アンスロビンP、⑯ヒスタグロビン、⑰アルブミン20%化血研*、⑱アルブミン5%化血研*、⑲静注グロブリン*、⑳ノバクトF*、㉑アンスロビンP1500注射用
報告企業の意見	レプトスピラ症は、病原性レプトスピラ感染に起因する人獣共通の細菌(スピロヘータ)感染症である。レプトスピラは通常、長さ 6～20μm、直径 0.1μm のらせん状の細菌で、病原性レプトスピラと非病原性レプトスピラに大別される。病原性レプトスピラは、げっ歯類をはじめ多くの野生動物や家畜(ウシ、ウマ、ブタ、ヒツジなど)、ペット(イヌ、ネコなど)の腎臓に保菌され、尿中に排出される。ヒトは、保菌動物の尿で汚染された水や土壌から経皮的あるいは経口的に感染する。レプトスピラ症は急性熱性疾患であり、感冒様症状のみで軽快する軽症型から、黄疸、出血、腎障害を伴う重症型(ワイル病)まで多彩な症状を示す。レプトスピラは現在、13 の遺伝種からなり、さらに免疫学的性状により 250 以上の血清型に分類されている。日本におけるレプトスピラ症の患者数は近年激減したが、南西諸島・本土南部地域では他の地域に比べて多く散発している。また世界的に見ると、特に東南アジアや中南米などの亜熱帯、熱帯地域で患者発生が多い。レプトスピラは感染初期にヒトの血液や尿から直接観察される場合があることから、本剤の原料への混入を完全に否定できないと考え、本報告を行った。 仮に、製造原料にレプトスピラが混入していたとしても、弊所で製造している全ての血漿分画製剤の製造工程には、約 0.2μm の「無菌ろ過工程」および、レプトスピラよりも小さいウイルスの除去を目的とした平均孔径 19nm 以下の「ウイルス除去膜ろ過工程」が導入されており、これらの工程により除去されるものと考えられる。更に、これまでに当該製剤によるレプトスピラ感染の報告例は無い。 以上の点から、当該製剤はレプトスピラ感染に対する安全性を確保していると考える。しかし、今後とも関連情報の収集に努め、本剤の安全性の確保を図っていきたい。

*現在製造を行っていない

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Arenal, a new *Leptospira* serovar of serogroup Javanica, isolated from a patient in Costa Rica

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ABSTRACT

Leptospirosis is a worldwide distributed zoonotic disease caused by pathogenic spirochetes of the genus *Leptospira*. The basic taxon of *Leptospira* is the serovar. Currently, nearly 300 serovars have been identified. Leptospirosis is particularly prevalent in warm and humid tropical regions where conditions for transmission and survival of pathogenic leptospires in the environment are optimal. Leptospirosis probably constitutes a serious veterinary and public health problem in Central America but solid figures are missing. To determine distribution of leptospirosis in Costa Rica and to identify locally circulating pathogenic serovars, we performed a sentinel-based study, isolating and characterizing leptospires from patients attending hospitals. Strain MAVJ 401 was isolated from a hospitalized patient in the Alajuela province. The isolate produced agglutination titers notably with reference rabbit antisera against serovars of serogroup Javanica but appeared serologically unique in the standard Cross Agglutinin Absorption Test. Therefore, MAVJ 401 was considered to represent a new serovar, designated Arenal, of the serogroup Javanica. Genotypic analysis revealed that strain MAVJ 401 belongs to *Leptospira santarosai*, a species that almost exclusively occurs in Latin America. This is not a unique finding of an exotic serovar. Recent isolates from severely ill patients in the same region appeared to be identical to Arenal.

We have identified a novel highly virulent serovar from a patient in Costa Rica that is common in this area, thus posing a threat for the local public and veterinary health.

1. Introduction

Leptospirosis is a worldwide zoonosis, transmitted to humans through contaminated water or direct exposure to the urine of infected animals. Human infection may be acquired through occupational, recreational, or avocational exposures. Direct contact with infected animals accounts for most infections in farmers, veterinarians, abattoir workers, meat inspectors, rodent control workers and other occupations which require contact with animals. Indirect contact is important for sewer workers, miners, soldiers, septic tank cleaners, fish farmers, gamekeepers, canal workers, rice field workers, taro farmers, banana farmers and sugar cane cutters (Levett, 2001).

The clinical spectrum of the disease ranges from mild influenza-like to severe forms such as the Weil's syndrome, characterized by hepato-renal dysfunctions and a bleeding tendency and Acute Respiratory Distress Syndrome (ARDS) with mortality rates exceeding 50% (Levett, 2001; McBride et al., 2005).

Development of a subclinical infection or clinical disease might depend on both host and causative agent related factors such as immunological competence, age, physical condition and virulence and size of the inoculum, respectively. Animals with subclinical infections as well as those that recover from the clinical disease become a potential source of infection for other susceptible hosts, because they continue to excrete leptospires for a prolonged period of time (Faine, 1982; Faine et al., 1999).

The causative agents of leptospirosis belong to the genus *Leptospira*, which contains both saprophytic and pathogenic species (Levett, 2001). The isolation and identification of an infecting *Leptospira* strain is cumbersome and time consuming. Isolation is difficult due to the slow growth rate, notably when combined with a concomitant contamination with faster growing microorganisms, and stringent and fastidious in vitro culture requirements of these bacteria (Faine, 1994; Faine et al., 1999). The

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initial identification of a *Leptospira* is morphological, by dark field microscopy observation. Definitive identification of the isolates requires the use of serological and molecular techniques (Dikken and Kmety, 1978; Brenner et al., 1999; Levett, 2003). In the conventional classification system, all pathogenic leptospires belong to the species *Leptospira interrogans* sensu lato (Dikken and Kmety, 1978; Faine and Stallman, 1982). Based on serological criteria, strains of *Leptospira* are differentiated into serovars, which represent the basic taxon (ICSB Sub-committee on the taxonomy of Leptospira, 1987; Kmety and Dikken, 1993). Serovars that are antigenically related are placed into serogroups. Serogroups do not have an official taxonomic status, but are of clinical and epidemiological importance (Levett, 2003). The list is updated periodically and more than 250 pathogenic serovars arranged in 26 serogroups are currently known. The recent genotypical classification system is based on DNA homology. In this system, leptospires are placed into 17 *Leptospira* species of a pathogenic, saprophytic and doubtful nature (Yasuda et al., 1987; Perolat et al., 1998; Brenner et al., 1999; Levett et al., 2006). There is a poor correlation between the serological and genotypic classification systems (Brenner et al., 1999; Yasuda et al., 1987).

The species *Leptospira santarosai* contains 61 serovars of multiple serogroups (Brenner et al., 1999). The type strain of *L. santarosai*, serovar Shermani strain 1342 K was isolated from a spiny rat (*Proechymis semispinousus*) in the Panama Canal Zone (Yasuda et al., 1987). Several additional reports confirmed that *L. santarosai* is pathogenic for humans and domestic animals (Brenner et al., 1999; Hsieh and Pan, 2004; Rossetti et al., 2005).

In this paper, we describe a new leptospiral serovar belonging to the species *L. santarosai* isolated from the blood of a severely ill leptospirosis patient.

2. Materials and methods

2.1. Case description

A 45-year-old man was hospitalized in Ciudad Quesada San Carlos Hospital, Costa Rica, with a 3–4 day history of fever, headache and myalgia. The patient is a biologist employed by a Costa Rican fish farm. At the day of admission his temperature was 39°. He had tachycardia and his blood pressure was 120/60 mmHg. Clinical examination showed a conscious man, with bilateral headache, sore throat, provoked myalgia of the legs, hepatalgia, hepatomegaly, and conjunctivitis. There were no signs of rash, meningeal irritation and cervical rigidity. Laboratory tests revealed increased SGOT:79.8 U/L (normal range (nr) 12.0–46.0), 76.2 U/L (nr 3–50), creatine phosphokinase: 915 U/L (nr 24–195), direct bilirubin: 0.53 mg/dL (nr 0.0–0.2), total bilirubin: 1.49 mg/dL (nr 0.0–1.0), associated with hyperglycemia: 143 mg/dL, alkaline phosphatase: 202 U/L (value is within normal range, nl), albumin: 3.3 g/dL (nl), and protein levels: 5.92 g/dL (nl), ureic nitrogen: 8.62 mg/dL (nl), creatinine: 1.26 mg/dL (nl). The leukocyte count was 8, $2 \times 10^3/\mu L$ with 80% polymorph nuclear forms. Thrombocytopenia: $145 \times 10^3/\mu L$ (last control: $99 \times 10^3/\mu L$) was also observed. Results of urinalysis were normal. Malaria blood smears, blood cultures and serology for dengue were negative.

The patient received a 7-day treatment with penicillin, 2 million units 4 times a day, which resulted in a resolution of symptoms. Oral treatment with penicillin was continued for 6 more days.

Leptospirosis was confirmed by seroconversion in the Microscopic Agglutination Test (MAT) with a titer of 1:100 with serovar Canicola in the second sample. Also the rapid screening test Lepto dipstick (Gussenhoven et al., 1997) gave a positive outcome (data not shown).

2.2. Bacterial culture

Culturing was performed in Ellinghausen and McCullough modified Johnson and Harris (EMJH) culture medium (DifcoTM). Aliquots of 0.1 and 0.01 mL of heparin anticoagulanted whole blood were inoculated into 6 mL EMJH culture medium. Incubation was at 30 °C and cultures were inspected by darkfield microscopy for growth of leptospires at regular intervals. Isolates were subcultured and maintained in EMJH medium and in Fletcher medium supplemented with 5 fluoro-uracil (200 μg/mL) as a selective inhibitor for contaminating microorganisms (Faine and Stallman, 1982; Faine et al., 1999; Hartskeerl et al., 2006).

2.3. Microscopic agglutination test

The microscopic agglutination test (MAT) was performed as per standard procedure (Comisión Cientifica Permanente sobre Leptospirosis de la AAVL, 1994) starting with a serum dilution of 1:20 up to 1:20480. The highest dilution of serum showing 50% reduction in free-moving leptospires under dark field microscope was considered the end-titre. Rabbit anti-*Leptospira* sera were prepared following the standard procedure (ICSB Sub-committee on the taxonomy of *Leptospira*, 1984).

2.4. Serological typing: MAT with group sera and monoclonal antibodies

To identify the isolate up to serogroup level, MAT was performed following standard procedure using a panel of 38 anti-*Leptospira* rabbit antibodies (Dikken and Kmety, 1978; Hartskeerl et al., 2006). Isolates were further typed at the serovar level by performing MAT with panels of monoclonal antibodies (mAbs) that characteristically agglutinate serovars from the serogroups Icterohaemorrhagiae and Sarmin (F12C3, F20C3, F20C4, F52C1, F52C2, F70C4, F70C7, F70C13, F70C14, F70C20, F70C24, F70C26, F82C1, F82C2, F82C7, F82C8, F89C3, and F89C12) as described by Korver et al. (1988) and from serogroup Javanica (F12C3, F20C3, F20C4, F70C20, F98C4, F98C5, F98C8, F98C12, F98C17, F98C19 and F98C20) with cross-agglutinations of serovars of the closely related serogroups Sarmin and Celledoni (Alex et al., 1993).

2.5. Cross Agglutinin Absorption Test

The Cross Agglutinin Absorption Test (CAAT), the standard assay for serological classification of *Leptospira* serovars was carried out by staff of INCIENSA as described elsewhere (Dikken and Kmety, 1978; Kmety and Dikken, 1993; Hartskeerl et al., 2006, ICSB Sub-committee on the taxonomy of *Leptospira*, 1984). Staff of the WHO/FAO/OIE Collaborating Centre for Reference and Research on Leptospirosis of the Royal Tropical Institute, The Netherlands confirmed the CAAT results.

2.6. Genetic characterization

Strains and isolates were grown at 30 °C in EMJH medium and harvested by centrifugation during the late logarithmic phase. DNA was isolated as described by Boom et al. (1990). PCR was performed on the DNA extracts using the primer set G1/G2 that specifically amplifies a 285 bp fragment of the *secY* gene from all pathogenic species except *L. kirschneri* (Gravekamp et al., 1993; Oliviera et al., 2003). PCR conditions and controls were as previously described (Gravekamp et al., 1993; Bal et al., 1994). PCR products were analyzed by electrophoresis in 1.5% agarose gels, stained with ethidium bromide using standard procedures and subsequently judged by eye under UV illumination.

For sequencing, DNA concentration of PCR products was adjusted in the range of 10–20 ng per reaction and applied to

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the sequence reaction using the BigDye® Terminator V1.1 Cycle Sequencing Kit (Applied Biosystems, United Kingdom) and subsequently analyzed on an ABI PRISM™ 310 Genetic Analyzer (Applied Biosystems, United Kingdom). DNA sequence clustal alignments were done using the LaserGene software package (DNASTAR). Species determination was done on basis of highest sequence identity of PCR products from *Leptospira* reference strains (Gravekamp et al., 1993; Oliviera et al., 2003; Rossetti et al., 2005; Priya et al., 2007).

3. Results

3.1. Isolation

The culture with 0.1 mL blood inoculation became positive after two weeks. The isolate was named strain MAVJ 401. Under the darkfield microscope, strain MAVJ 401 showed typical *Leptospira* motility and morphology. The strain grew well in EMJH and Fletcher medium at 30 °C.

3.2. Serological characterization

When testing the strain against a panel of 38 rabbit anti-*Leptospira* sera to determine potential serogroups, highest agglutination titers were found against serogroup Sarmin serovar Weaveri and serogroup Javanica serovar Poi. Low cross-agglutinating titers were also produced with members of the serogroups Icterohaemorrhagiae and Celledoni. No agglutinations were found with reference sera from intermediate and saprophytic reference strains, suggesting a pathogenic status of the isolate.

Subsequent testing with the panel of mAbs against serovars of the Icterohaemorrhagiae and Sarmin groups only revealed a titer 1:320 against one of the 18 mAbs in the panel. No match was found with the agglutination pattern of any of the serovars in these two serogroups (results not shown). The agglutination pattern obtained with the mAbs against serovars of the Javanica group was most similar with that of serovar Javanica, strain Veldrat Batavia 46 (Table 1). No match was found with serovars of the closely related serogroup Celledoni and, again, serogroup Sarmin.

Cross-agglutinations and CAAT were performed to confirm the presumptive results obtained via mAbs typing.

Cross-agglutination experiments were executed between strain MAVJ 401 and antiserum against all serovars from the groups Javanica, Sarmin and Celledoni and vice versa. No significant cross-agglutinations (>10% compared to the homologous agglutination) were observed with sera from the serogroups Celledoni and Sarmin and vice versa, serum against MAVJ 401, virtually excluding that MAVJ 401 belongs to these serogroups. A significant cross-agglutination titer in both cross-agglutination experiments was only found against serogroup Javanica serovar Fluminense strain Aa3. Surpisingly only low cross-agglutination titers were found against serovar Javanica strain Veldrat Batavia 46.

Table 1
Comparison of agglutination titers of strain MAVJ 401 and the reference serovar Javanica, strain Veldrat Batavia 46 with mAbs against serogroup Javanica

mAb	Reciprocal titers against strain MAVJ 401	Reciprocal titers against strain Veldrat Batavia 46
F12C3	–	–
F20C3	–	–
F20C4	320	320
F70C20	–	–
F98C4	–	–
F98C5	–	–
F98C8	5120	5120
F98C12	20480	5120
F98C17	–	–
F98C19	10240	10240
F98C20	–	≤80

(–) No agglutination.
Up to a 4-fold titer difference is acceptable in mAbs typing.

Table 2
Cross-agglutinations and CAAT between MAVJ 401 and reference strains

Serum	Strain	Cross agglutination (%)[a]	CAAT, residual titer (%)[b]
Aa3	MAVJ 401	50	50
MAVJ 401	Aa3	12.5	100
Sofia 874	MAVJ 401	12.5	50
MAVJ 401	Sofia 874	0.2	ND
Cox	MAVJ 401	6.25	50
MAVJ 401	Cox	0.4	ND
Veldrat Batavia 46	MAVJ 401	1.5	100
MAVJ 401	Veldrat Batavia 46	0.2	ND
Sorex Jalná	MAVJ 401	100	100
MAVJ 401	Sorex Jalná	0.2	ND
L 82	MAVJ 401	12.5	100
MAVJ 401	L 82	0.8	ND
MMD 3	MAVJ 401	50	100
MAVJ 401	MMD 3	6.25	ND
Rr 5	MAVJ 401	25	50
MAVJ 401	Rr5	6.25	ND
CZ 390	MAVJ 401	25	100
MAVJ 401	CZ 390	1.5	ND

[a] (Heterologous titer: homologous titer) × 100%; >10% is significant.
[b] (Homologous titer after absorption: homologous titer before absorption) × 100%; <10% indicates similarity of the serovars.

CAAT was performed in duplicate and independently by two persons to assure reproducibility. The following reference strains were included in the test, Javanica group; serovar Fluminense strain Aa3, serovar Sofia strain Sofia 874, serovar Coxi strain Cox, serovar Javanica strain Veldrat Batavia 46, serovar Sorexjalna strain Sorex Jalná, serovar Zhengkang strain L 82 and serogroup Sarmin; serovar Machiguenga strain MMD 3, serovar Rio strain Rr 5 and serovar Weaveri strain CZ 390.

According to the definition of the International Committee on Systematic Bacteriology, Subcommittee on the Taxonomy of *Leptospira* (1984, 1987), strain MAVJ 401 was not serologically identical to any of these strains (Table 2) and therefore MAVJ 401 represents a new serovar, designated Arenal. Based on the initial serological reactions it is proposed that this serovar is placed within the pathogenic serogroup Javanica.

3.3. Species determination

Consistent with its pathogenic status, DNA from MAVJ 401 was amplified by primer pair G1/G2 (Gravekamp et al., 1993). To determine the species of MAVJ 401, the sequence of its G1/G2 amplicon was compared with 65 other sequences (Oliviera et al., 2003; Rossetti et al., 2005; Priya et al., 2007). The sequence of the amplicon showed highest percentage identity with a number of strains from *L. santarosai*, i.e. 97.1% with serogroup Sejroe; serovar Caribe strain TRVL 61866 and serovar Gorgas strain 1413 U, serogroup Mini; serovar Georgia strain LT 117 and Tabaquite strain TRVL 3214, serogroup Pyrogenes; serovar Princestown strain TRVL 112499, serogroup Javanica; serovar Vargonis strain 24, serogroup Sarmin; serovar Weaveri strain CZ 390 and 96.7% identity with serogroup Pomona, serovar Tropica strain CZ 299.

Percentages sequence identity outside *L. santarosai* ranged from 71.3% (*L. meyeri*, serovar Semaranga strain Veldrat Semarang 173) to 94.7% (*L. weilli* serovar Mengrun strain A 102 and *L. weilii*, serovar Coxi strain Cox). Taking the highest percentage of identity with eight strains of *L. santarosai*, we believe that MAVJ 401 belongs to this species.

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4. Discussion

We describe the isolation and characterization of a novel *Leptospira* serovar isolated from a Costa Rican patient. The patient was admitted to the hospital with signs and symptoms compatible with leptospirosis and standard antibiotic treatment with penicillin was effective. Leptospirosis was serologically confirmed. It likely concerns here an occupational disease as the patient worked on a fish farm where he obviously acquired the infection via fish ponds contaminated with urine of carrier animals.

The morphology and motility of the bacterium under darkfield microscopy is consistent for the genus *Leptospira*. Serologically, the isolate showed titers notably against members of the serogroups Javanica and Sarmin. Cross-agglutination titers were also found in the serogroups Icterohaemorrhagiae and Celledoni. This likely represents intra-serogroup cross-agglutinations because serogroups Javanica and Celledoni on one hand and Javanica, Sarmin and Icterohaemorrhagiae on the other hand form 'serogroup complexes' comprising antigenic related serovars (Hartskeerl et al., 2006). Because of this overlapping antigenic relationship between these groups and the fact that highest agglutinating titers were produced with serovars of serogroup Javanica we suggest to place MAVJ 401 into this serogroup.

We found contrasting data by mAbs typing and the CAAT. mAbs typing generated a pattern that was highly similar to that of the reference serovar Javanica strain Veldrat Batavia 46 of the Javanica group. However, cross-agglutination and CAAT revealed only little similarity with this serovar. Moreover, CAAT, which is the standard method to determine the serovar as basic taxon, revealed that this isolate is unique. The serovar status is mainly, if not exclusively, based on the composition and structure of the highly antigenic LPS (Faine et al., 1999). A likely explanation of the discrepancy in typing with monoclonal and polyclonal sera is that panels of agglutinating mAbs are directed to a limited number of epitopes while polyclonal hyperimmune sera cover the full spectrum of epitopes. Apparently, it is possible that a set of mAbs recognizes a limited number of common epitopes on furthermore different LPS in distinct serovars within a serogroup. As shown in this study, incorrect mAbs-based identification can be avoided by determining cross agglutination with polyclonal hyperimmune serum against the presumably corresponding reference strain.

We designated the isolate serovar Arenal after the volcano in the Costa Rica near the residence of the patient in the province Alajuela.

DNA sequence analysis indicated that serovar Arenal most likely belongs to species *L. santarosai*, which is distributed almost exclusively in Latin America (Chappel et al., 1998).

Serovar Arenal likely is not an exotic serovar and might be common in and around the Alajuela province of Costa Rica. Recently, two out of 21 isolates obtained from Costa Rica were identified as serovar Arenal implying that 13.6% (3/22) of the isolates consisted of Arenal. The two additional Arenal isolates, preliminary coded as isolate 7 and 11, were cultured from severely ill patients living in the Puntarenas province that flanks Alajuela. Molecular analysis of MAVJ 401/isolate 7 by Multilocus Sequence Typing showed that it formed a distinct branch that was positioned closely to, but apart from the clade of *L. santarosai* (Ahmed et al., 2006). This supports the unique character of this novel serovar, also on genotypical grounds.

The infection source of isolate 11 is unknown. Infection with isolate 7 was very likely acquired via contact with cattle. The environment of the fish farm of MAVJ 401 makes it possible that the ponds have been contaminated with urine of infected cattle. It is therefore tempting to speculate that cattle form the infection reservoir of this novel serovar. However, further research on potential infection sources in the region will be needed to confirm or refute this.

L. santarosai, serovar Arenal, type strain MAVJ 401 has been deposited under this designation in the culture collections of the National Reference Center for Leptospirosis, Costa Rican Institute for Research in Nutrition and Health, Tres Ríos, Costa Rica and the WHO/FAO/OIE and National Collaborating Centre for Reference & Research on Leptospirosis, Royal Tropical Institute, Amsterdam, Netherlands. The novel serovar designation of strain MAVJ 401 has been ratified by the International Committee on Systematic Bacteriology, Subcommittee on the Taxonomy of *Leptospiraceae*.

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識別番号・報告回数		回	報告日 年　月　日	第一報入手日 200 年 4 月 10 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	Portsmouth woman's death under investigation dailypress.com, April 11, 2008	公表国 米国	
販売名（企業名）						

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
異型クロイツフェルト・ヤコブ病(vCJD)に関連すると疑われる脳変性疾患を呈した米国の女性の症例が報告された。しかし，感染症，脳内酸素欠乏，肝不全，腎不全，毒物暴露，代謝疾患，脳腫瘍，頭蓋内圧の上昇，栄養不足など多数の原因が，本症例の脳疾患に関連していると考えられており，原因究明には更なる調査が必要である。MRI 又は脳スキャンの結果が，アトランタの疾病対策センターに送付され，バージニア大学及び National Prion Disease Pathology Surveillance Center (NPDPSC) で更に調査されることになっているが，結果が出るまでには数ヶ月間を要すると考えられている。	BYL-2008-0316

報告企業の意見	今後の対応
弊社の血漿分画製剤は米国の血漿を使用しているが，現在までに報告されている米国での vCJD 3 例は，米国以外の国で暴露された患者に限定されている。また，弊社の血漿分画製剤の製造工程におけるプリオン除去能は 4 log を上回ることが確認されており，弊社製剤による vCJD 感染リスクは極めて低いと考えられる。	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。

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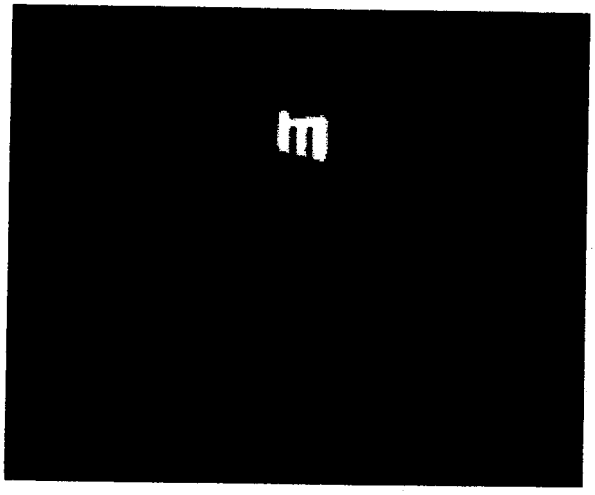
Portsmouth woman's death under investigation

By VERONICA GORLEY CHUFO

247-4741

April 11, 2008

RICHMOND



The illness and Wednesday death of a Portsmouth woman spurred a Virginia Department of Health investigation Thursday.

The woman suffered from encephalopathy, a degenerative brain disease. Her illness has been linked in news reports to variant Creutzfeldt-Jakob Disease — the human form of mad cow disease.

It's a very rare condition related to the consumption of beef infected with bovine spongiform encephalopathy. It's always fatal, the health department said in a news release.

The woman's name was not released by the health department but news reports have identified her as Aretha Vinson.

The illness could have been caused by a number of things, State Health Commissioner Karen Remley said in the release.

"Infections, lack of oxygen to the brain, liver failure, kidney failure, toxic exposures, metabolic diseases, brain tumors, increased intracranial pressure and poor nutrition are all related to encephalopathy," Remley said. "Further testing is the only way to know what caused this illness."

An MRI, or brain scan, was sent to the Centers for Disease Control and Prevention in Atlanta. Additional tests will be handled by the University of Virginia and the National Prion Disease Pathology Surveillance Center in Cleveland. Results are expected to take several months.

At least 200 cases of variant Creutzfeldt-Jakob Disease have been reported worldwide since 1996. Three cases have been reported in U.S. residents, and they were all exposed outside the country, Remley said. It's not spread casually from person to person.

For more information, visit cdc.gov, cjdfoundation.org or vdh.virginia.gov.