strains currently circulating in North America. This region of the protein has been assigned to antigenic sites (*17*) and has been associated with adaptation to growth in eggs (*18*). Phylogenetic analysis showed that each of the 8 viral genes of A/Canada/1158/2006 clustered with A/swine/Ontario/33853/2005 (H3N2) and other swine/turkey Canadian isolates from 2005. Although the HA gene of these isolates were shown to be closely related to American viruses that were first isolated from pigs in 1999, they represent a new distinct cluster (*2*). The NA genes are phylogenetically distinct from the US swine isolates and are represented by human influenza (H3N2) isolates from Asuncion, Paraguay (2001), and New York (2003) (*2*).

A recent review described 50 cases of symptomatic human infection with SIV, documented in the literature through April 2006; 46 cases were infected with subtype H1N1 and 4 were infected with subtype H3N2 (*19*). The spectrum of pathogenicity of SIV infection ranges from asymptomatic infection (*6*) to death; 7 of these 50 patients died (*5,20–24*). Laboratory-confirmed swine influenza in humans may be "the tip of the iceberg." Diagnosis of the current case was serendipitous because typing was performed only because the case occurred outside of influenza season.

The mode of spread of SIV in humans is not established. Because of his young age, the index patient was not likely to have had unrecognized direct contact with swine. That aerosolization of influenza virus occurs is increasingly recognized (*25*), but the child was reportedly never in the barns that housed the swine. However, other members of the farm reported that infants were sometimes taken for walks through the barn. The child also may have acquired the virus from person-to-person spread or from fomites. All 13 patients in the Fort Dix outbreak and 15 of 37 previously reported civilian case-patients also had no swine contact (*19,20*).

The Fort Dix outbreak of SIV in humans lasted only 21 days and never spread outside the military base. The calculated basic reproductive rate (R_0) was only 1.1 to 1.2. This suggests that person-to-person spread of the implicated H1N1 strain was not efficient enough to produce a major epidemic (*26*). However, future strains of SIV could have a higher R_0, and documentation of a case of swine influenza (H3N2) in a child with unrecognized transmission within the community adds another possible mechanism by which major epidemics of influenza could arise. Swine influenza infection in humans most commonly results in either no symptoms or a self-limited illness (*6*). However, routine surveillance for cases among swine workers may enable early detection of a strain with the potential for person-to-person transmission, prompting institution of infection control measures and vaccine development.

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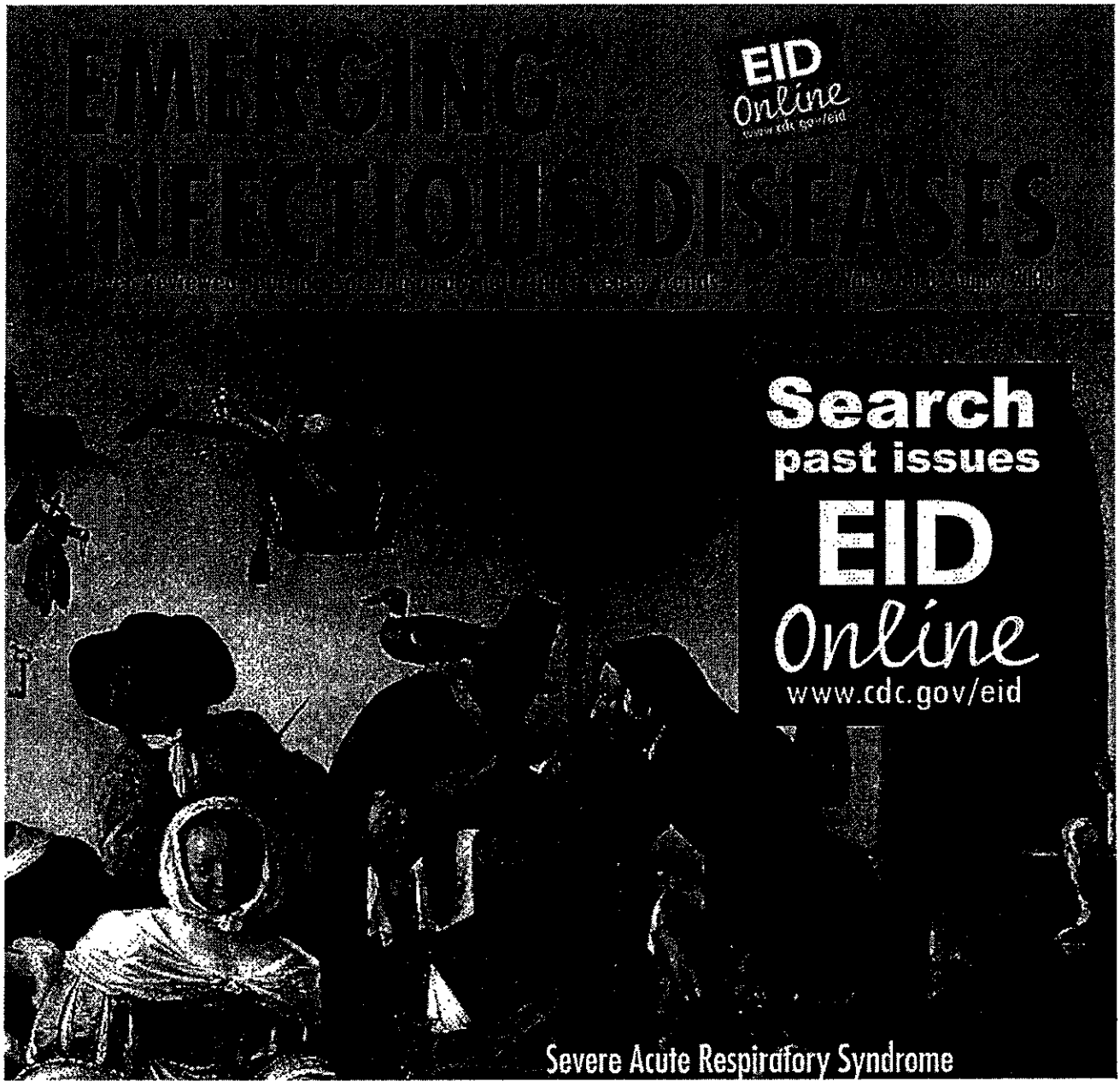

別紙様式第2

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医薬品　研究報告　調査報告書

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一般的名称			研究報告の公表状況	Clinical and virological characterization of persistent human infection with simian foamy viruses. AIDS research and human retroviruses, Nov 2007, 23	公表国 米国	
販売名（企業名）	タココンブ（CSL ベーリング株式会社）					

研究報告の概要 91

問題点（SFV 感染者は輸血や移植）

HIV と HTLV の病原性のレトロウイルスは、非ヒト霊長類から SIV と STLV のヒトへの感染が定着し、人から人への感染が拡大した。simian foamy viruses (SFV) 感染は、捕獲された非ヒト霊長類間でかなり伝播している。職業上非ヒト霊長類やその体液と接触したり、岐まれたり、引掻かれた人達に SFV 感染が確認されてきた。遺伝子配列を解析すると、人への SFV 感染はチンパンジー、ヒヒ、アフリカサバンナモンキーなど多様な非ヒト霊長類を起源としていることが分かっている。

筆者らは、SFV 感染した人 13 名の中で 7 名を長期追跡調査した。遺伝子配列を解析すると、SFV は参加者 2 名がヒヒ由来であり、他の 5 名はチンパンジー由来であった。

参加者 7 名は、非ヒト霊長類やその唾液、尿などの体液に接する機会があり、体液が参加者の皮膚と粘膜と暴露したり、皮膚損傷があると報告している。

全ての参加者の抹消血単核球（PBMC）から SFV DNA が検出され、口腔の検体、尿、精液からも検出された。

自己申告による健康状態を検討したが、SFV 感染と関連がある共通した臨床的な症候群は示唆できなかった。

臨床検査を調べ最も興味ある事は、参加者 3 名で好酸球減少、血小板減少の軽度の異常があったことである。しかし臨床上重要ではない。

参加者 3 名の妻を SAV 感染者との接触者として、ウエスタンブロット法と PCR 法で調べたが陰性であった。少人数での限られた追跡調査期間での観察のため、SFV 感染に関連する病状や人の二次的 SFV 感染は特定できなかった。

筆者らは、人における感染は医学的に重要性が解明されていないので、SFV 感染者は輸血や移植を控えるべきであると警告している。

使用上の注意記載状況・その他参考事項等

報告企業の意見	今後の対応
SFV 感染の人での病態や二次感染について明確になっていない。SFV はレトロウイルスであることから、本剤の製造工程で不活化できると考えられる。	今後とも情報収集に努める所存である。

(4)

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Clinical and Virological Characterization of Persistent Human Infection with Simian Foamy Viruses

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ABSTRACT

Persons occupationally exposed to nonhuman primates (NHPs) can be persistently infected with simian foamy virus (SFV). The clinical significance and person-to-person transmissibility of zoonotic SFV infection is unclear. Seven SFV-infected men responded to annual structured interviews and provided whole blood, oral, and urogenital specimens for study. Wives were tested for SFV infection. Proviral DNA was consistently detected by PCR in PBMCs of infected men and inconsistently in oral or urogenital samples. SFV was infrequently cultured from their PBMCs and throat swabs. Despite this and a long period of intimate exposure (median 20 years), wives were SFV negative. Most participants reported nonspecific symptoms and diseases common to aging. However, one of two persons with mild thrombocytopenia had clinically asymptomatic nonprogressive, monoclonal natural killer cell lymphocytosis of unclear relationship to SFV. All participants worked with NHPs before 1988 using mucocutaneous protection inconsistently; 57% described percutaneous injuries involving the infecting NHP species. SFV likely transmits to humans through both percutaneous and mucocutaneous exposures to NHP body fluids. Limited follow-up has not identified SFV-associated illness and secondary transmission among humans.

INTRODUCTION

TWO PATHOGENIC RETROVIRUSES, human immunodeficiency virus (HIV) and human T-lymphotropic virus (HTLV), established endemicity in human populations following infection of individual humans with simian immunodeficiency viruses (SIV) and simian T cell lymphotropic viruses (STLV) from nonhuman primate (NHP) reservoirs, respectively, and viral adaptation facilitating human-to-human spread.[1] Continued direct contact between human and NHPs in occupational and other settings provides an ongoing opportunity for introduction of additional simian retroviruses across species into human populations.

Foamy viruses (FVs), retroviruses in the *Spumavirus* genus,[2,3] establish persistent infections endemic to many mammalian species. Simian FV (SFV) infection is highly prevalent among captive NHPs.[4–6] Despite SFV coevolving with primates for at least 30 million years,[7] endemically infected human populations have not been identified.[6] A prototype FV (PFV), previously termed "human" FV (HFV) because it was isolated from a nasopharyngeal carcinoma (NPC) from a Kenyan man in 1971,[8] is now known to be of chimpanzee origin.[9,10] SFV infections have been identified in persons exposed directly to NHPs and their body fluids occupationally or through hunting, butchering, or habitat sharing.[10–16] Sequence analysis suggests

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that these human SFV infections originated from multiple NHP species, including chimpanzee, baboon, African green monkey, macaque, De Brazza's guenon, mandrill, and gorilla.[4,6,10] Putative associations between FV infection and various human diseases, including NPC, have not been supported in well-designed studies.[6,17,18]

Unlike HIV and HTLV, the clinical significance and secondary transmissibility of human infections with SFV are unknown. SFV is strongly cytopathic in human and NHP cells *in vitro*,[6] but is not recognized to be associated with disease in any natural host, though this has not been systematically evaluated. SFVs are easily transmitted between NHPs, mostly by contact with oral secretions during grooming or biting.[5,6]

Surveillance for simian retrovirus infection in persons occupationally exposed to NHPs at research centers and zoos in North America identified 14 persons with serological evidence of SFV infection.[10,12] Using archived sera, most workers were shown to have long-standing zoonotic infection with unclear exposure risks or public health significance [10,12] We report preliminary results from the first prospective cohort study of persons persistently infected with SFV. We characterize the potential for secondary transmission by determining the presence of virus in various body fluids and by longitudinal testing of intimate contacts, evaluate the health status of humans persistently infected with SFV, and assess possible occupational risk exposures leading to infection.

MATERIALS AND METHODS

Study design and enrollment

Persons with documented SFV infection identified through surveillance of occupationally exposed workers were eligible to provide informed consent and enroll as primary participants in a prospective cohort study approved by the Centers for Disease Control and Prevention (CDC) Institutional Review Board.[10,12] Documented SFV infection was defined as seroreactivity to SFV antigens by Western blot (WB) combined with evidence of proviral DNA sequences in peripheral blood mononuclear cells (PBMCs) by polymerase chain reaction (PCR) and/or isolation of SFV from PBMCs.[10,12]

Spouses/partners and children of SFV-infected humans or other persons living in the same household were also eligible to enroll as contact participants. Informed consent was obtained from all participants before enrollment. All enrollees were offered follow-up for a minimum of 5 years.

Participant interviews

Participants were interviewed by telephone at enrollment and annually for 5 years using a standard questionnaire. Information was collected on demographics and health status at the time of enrollment. Participants were asked about their general health status including personal health observations and conditions diagnosed by physicians and about symptoms known to be associated with retroviral infections such as malignancies or lymphoproliferative, inflammatory, and neurological diseases.[3] To evaluate exposure opportunity, information was collected on the duration of occupational exposure to specific NHP species, work activities and practices including use of protective equipment, past injuries, and specific exposures to NHP blood or body fluids. To identify opportunities for secondary transmission, participants were questioned about sexual contacts, practices, and other activities that may result in intimate exchange of body fluids, including donation of blood or other living biological material. Participants were counseled regarding current knowledge about human SFV infection and provided the opportunity to ask questions.

Specimen collection and preparation

Whole blood, parotid saliva, swabs of saliva and the posterior oropharynx ("throat swabs"), urine, and semen (all primary participants were male) were requested from participants annually for clinical, virological and immunological testing. Parotid saliva was collected in intraoral (Schaefer) cups and immediately transferred with a pipette to cryovials.[19] Throat and saliva swabs were collected with viral culturettes (Becton/Dickinson). Nonblood specimens were shipped to the CDC immediately after collection on wet ice; whole blood was shipped at room temperature.

Upon arrival at the CDC parotid saliva was centrifuged for 2 min at $1000 \times g$ and cell pellets and supernatant were aliquoted and frozen at $-80°C$ until tested. Throat and saliva swabs were placed in 2 ml phosphate-buffered saline (PBS), vortexed, and then centrifuged for 5 min at $1000 \times g$ to pellet any cells present. The cell pellet was washed twice with PBS, then divided equally for PCR testing and for tissue culture for some participants. Urine and, when available, semen samples were centrifuged for 10 min at $800 \times g$ to pellet any cells present and washed twice with PBS and stored at $-80°C$. Urine and semen supernatants were aliquoted and stored at $-80°C$ for mucosal immunity studies.[19]

Clinical laboratory testing

Clinical testing was performed by a commercial diagnostic laboratory. Clinical testing included complete blood counts (CBC) with differential analysis of white blood cells, testing of serum for electrolytes, glucose, creatinine, blood urea nitrogen, uric acid, total protein, albumin and globulin, total bilirubin, adenosine phosphatase, lactate dehydrogenase (LDH), serum aspartate aminotransferase (AST), and serum alanine aminotransferase (ALT).

Virological and immunological analysis

DNA lysates were prepared from PBMCs and from pelleted cells from parotid saliva, mixed saliva, throat swabs, and urine and tested for SFV polymerase (*pol*) proviral sequences using nested PCR.[10,12] DNA quality was confirmed by β-actin PCR as previously described.[10,12] Virus isolation was attempted from selected participant's PBMCs, throat, and saliva samples. Specimens were cultured on canine thymocytes and/or *Mus dunni* fibroblasts and monitored biweekly for up to 40 days for cytopathic effect, reverse transcriptase (RT) activity, and proviral *pol* sequences.[10,12]

Plasma was tested for SFV antibodies using a WB assay that can detect both monkey and ape SFV as described in detail elsewhere.[4,10,19,20] Saliva and urine were tested for the presence of anti-SFV IgG and IgA by WB analysis.[19]