J Med Primatol doi:10.1111/j.1600-0684.2010.00415.x

ORIGINAL ARTICLE

Tetraparesis resembling acute transverse myelitis in a captive chimpanzee (*Pan troglodytes*): long-term care and recovery

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Keywords
ape – decubitus ulcer – paralysis – paresis – pressure sore – pressure ulcer – primates – rehabilitation – spinal cord – wound care

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Accepted March 21, 2010.

Abstract

Background A 24-year-old, male chimpanzee (*Pan troglodytes*) developed acute tetraparesis. Magnetic resonance imaging showed a diffuse T2-weighted hyperintensive lesion, indicating inflammation at the C1–2 level. All infective, autoimmune, and vascular investigations were unremarkable.
Results and Conclusions The chimpanzee's condition most resembled acute transverse myelitis (ATM) in humans. The chimpanzee was in severe incapacitated neurological condition with bedridden status and required 24-hour attention for 2 months followed by special care for over a year. Initially, corticosteroid therapy was performed, and his neurological symptoms improved to some extent; however, the general condition of the chimpanzee deteriorated in the first 6 months after onset. Pressure ulcers had developed at various areas on the animal's body, as the bedridden status was protracted. Supportive therapy was continued, and the general condition, appetite, mobility, and pressure ulcers have slowly but synergistically recovered over the course of 2 years.

Introduction

The worldwide annual incidence of spinal cord injury (SCI) is estimated as 22 per million of the human population, and there are approximately 2.5 million SCI survivors in the world [23]. Although human patients with SCI suffer from handicaps that affect their quality of life considerably, their life expectancy is very good [23]. In contrast, handicapped animals are less likely to survive in the wild, and it is difficult to care for animals with such conditions in captivity, especially larger animals such as chimpanzees. Nevertheless, there have been several cases of chimpanzees surviving after contracting paralytic diseases. In 1966, when a paralytic disease, presumably poliomyelitis, broke out in the wild chimpanzee community in Gombe, Tanzania, six of ten affected individuals survived and adapted well to their various disabilities; some chimpanzees learned to walk long distances in the upright position [9]. In captivity, a 23-year-old male chimpanzee at the University of Texas was reported to have acute onset and subsequent recovery from flaccid tetraplegia that resembled inflammatory polyradiculoneuropathy, also known as Guillain–Barre syndrome in human beings [1]. There was a case of long-term care of a paralyzed juvenile chimpanzee caused by meningoencephalitis at Sanwa Kagaku Kenkyusho Co., Ltd., in Kumamoto, Japan (Udono, personal communication). After the onset of illness at the age of 11 months, the chimpanzee was cared for affectionately and survived in

bedridden status for 8 years. Other zoological or research institutions may have experienced such cases, but few cases of long-term care of a chimpanzee surviving after SCI have been documented.

Pressure ulcers are common in patients with SCI, despite widespread knowledge of the importance of ulcer prevention [21]. Pressure ulcers also occur in non-human primate models of SCI [6]. However, spontaneous pressure ulcers in non-human primates including chimpanzees have rarely been reported. To evaluate the pressure ulcers, several organizations have developed scoring systems [5, 11, 24, 26]. We attempted to use the 'DESIGN' tool recommended by the Japanese Society of Pressure Ulcers (JSPU) as a tool to evaluate especially the healing process of pressure ulcers, in addition to standard systems developed by National Pressure Ulcer Advisory Panel (NPUAP) in the U.S. and the European Pressure Ulcer Advisory Panel (EPUAP).

In this report, we describe a case of a SCI resembling acute transverse myelitis (ATM) in an adult male chimpanzee, focusing on the long-term care and the development and healing of pressure ulcers.

Case report

A 24-year-old, 57-kg male chimpanzee named 'Reo' at the Primate Research Institute, Kyoto University (KUPRI), developed acute onset of tetraparesis. The chimpanzee was kept in an indoor–outdoor enclosure where he led a social group consisting of two male and three female chimpanzees: see [16, 17] for further information of the groups. The chimpanzee was born in KUPRI and used in psychological research [7, 27]. He had no history of being used in medical research. No clinical signs were noted before the day of onset (day 1), and the results of blood examinations and intradermal tuberculin tests 1 year prior to the onset were unremarkable. When the chimpanzee was found lying on the ground, he was conscious but unable to move his body below the neck. He was immobilized with ketamine hydrochloride (HCl) (100 mg/ml Ketalar®, 3.5 mg/kg; Daiichi Sankyo Propharma., Tokyo, Japan) and medetomidine hydrochloride (Domitor®, 0.035 mg/kg; Meiji Seika Kaisha, Ltd., Tokyo, Japan) for physical examination and diagnostic testing. Anesthesia was maintained with isoflurane (Isoflu; Dainippon Sumitomo Pharma Co., Ltd., Osaka, Japan) delivered in oxygen through a precision vaporizer and a rebreathing circuit.

Physical examination showed that the chimpanzee was not seriously injured, his lymph nodes were normal, and his body temperature was 35.9°C. Complete blood count (CBC) revealed an elevated WBC count ($18.9 \times 10^3/\mu$l), >95% mature neutrophilia, and elevated Ht (61.4%). A serum chemistry and electrolytes panel indicated an elevated CPK (1428 U/l) and low levels of potassium (3.1 mEq/l). Spine radiographs showed neither spinal fracture nor compression. While the chimpanzee was under anesthesia, antibiotics ampicillin sodium and cloxacillin sodium (Viccillin® S1000, 1g, IM; Meiji Seika Kaisha, Ltd.), antitetanus serum (36000 IU, IM), and crystalloid solutions fluids (SOLDEM®1, IV; followed by SOLDEM®3A TERUMO CO., Tokyo, Japan) were administered as symptomatic treatments. Thiamine monophosphate disulfide, vitamins B6 and B12 (Vitamedin; Daiichi-Sankyo Co., Ltd., Tokyo, Japan), amino acids (Hy-Pleamin; Fuso Pharmaceutical Industries, Ltd., Osaka, Japan), and glucose (Otsuka glucose injection 20%; Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) were added to the fluids. The chimpanzee was fully alert when he recovered from anesthesia. He consciously reacted to the keepers' voice, and his cranial nerve appeared to be intact; eye movement, hearing, facial expression, deglutition, respiration, and tongue movement were normal. Voluntary movement of the limbs was not apparent, but when the limbs were touched, slight movement was observed. There was no evidence of atrophy. It was not possible to test precise spinal reflexes when the chimpanzee was alert, because he was not cooperative at the time of onset and it was not considered safe for the personnel to do the testing. Micturition and defecation appeared normal.

Results

MRI and CSF examinations

Cervical magnetic resonance images (MRIs; General Electrics Signa Profile MRI scanner, 0.2 T; GE Yokoo Medical Systems Co., Tokyo, Japan) were taken on the second day. The images were viewed and discussed with both veterinary and human neurologists. Diffused enhancement at the C1–C2 level (Fig. 1A) was evident on T2-weighted sagittal image consistent with inflammation. A high level of serum C-reactive protein (CRP) (4.8 mg/dl) and the results of cerebrospinal fluid (CSF) measurements (CSF protein 200 mg/dl, s.g. 1.008, cell count 1.7/μl, lymph cells 100%, glucose within normal range) on the second day also supported the presence of inflammation. MRIs were retaken 4 months (day 119) and 8 months (day 224) after the onset of the disease (Fig. 1B, C, respectively). The images in four and 8 months showed a spot that was hypointensive on T1-weighted sagittal image and

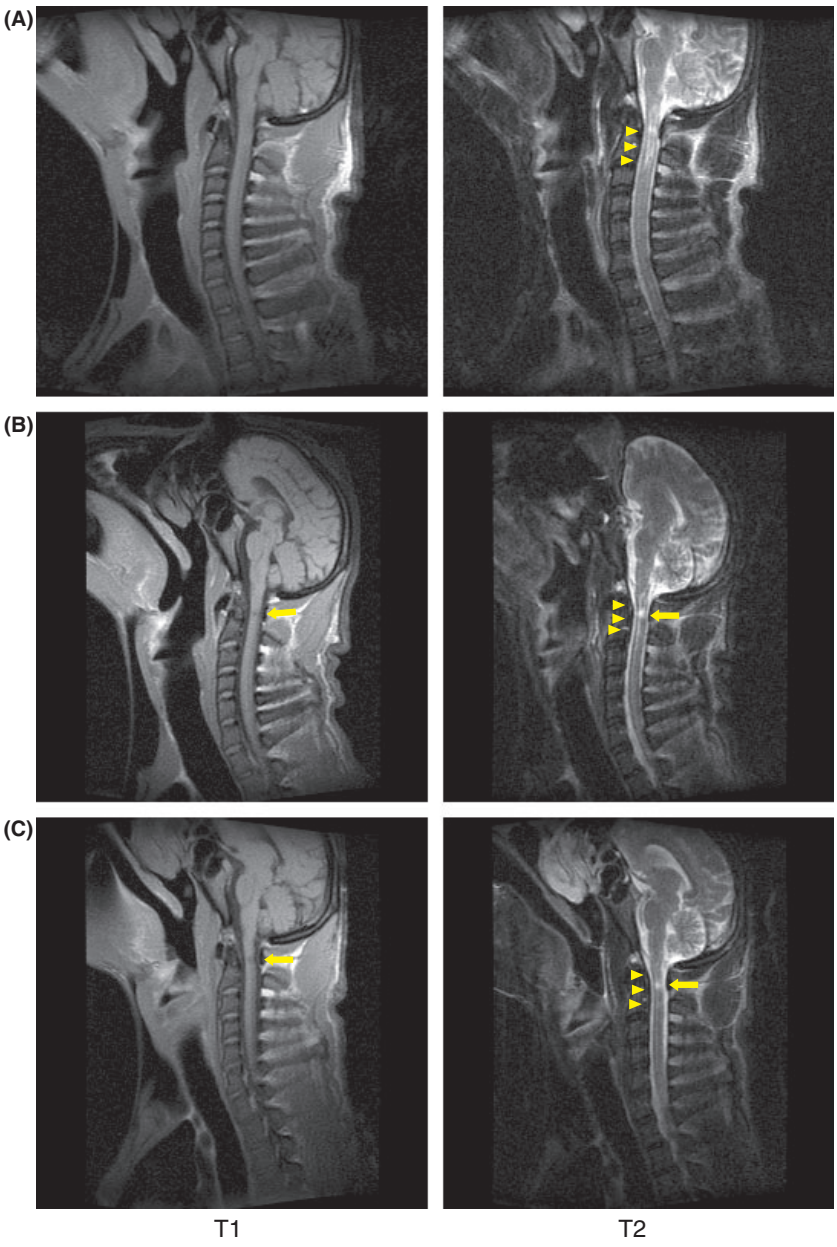

Fig. 1 (A) The MRI images on day 2 showing a diffuse T2-weighted hyperintensive lesion at the C1–2 level (arrow heads). The MRI images on day 119 (B) and 224 (C) showed a spot which was hypointensive on T1 and hyperintensive on T2-weighted sagittal image (arrows) and the diffused enhancement at C1–C2 level on T2 observed on the second day was reduced (arrow heads).

hyperintensive on T2-weighted sagittal image, and diffused enhancement at the C1–C2 level on the T2-weighted images observed on the second day was reduced. The results were interpreted as indicating that the initial inflammation had subsided and necrosis had occurred and remained at the affected spot.

Serological examinations

Serological studies gave negative results for herpes simplex, mumps, enterovirus, and hepatitis A, B, and C antibodies. The result for varicella zoster virus (VZV) antibodies was positive, which was also positive in other chimpanzees at KUPRI. The result for cytomegalovirus (CMV) antibodies was also weakly positive. The chimpanzees in the KUPRI were not vaccinated routinely against polio, tetanus, or rabies. Tetanus but not rabies or polio is present in the area. The antinuclear antibody was negative as well.

Treatments

The chimpanzee was treated with intravenous antibiotics (initially, ampicillin sodium and cloxacillin sodium

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(Viccillin S1000, Meiji Seika Kaisha, Ltd., Tokyo, Japan, and later selected antibiotics according to the sensitivity results) and high doses of dexamethasone (Decadron; Banyu Pharma. Co., Ltd., Tokyo, Japan) intermittently [the first term (days 3–6): iv administration of 9 mg qid for 1 day and 16 mg qid for 2 days; the second term (days 15–18): iv administration of 16 mg qid for 3 days; the third term (days 78–87): im administration of 8 mg dexamethasone qid for 3 days, followed by 4 mg qid for 3 days, then 2 mg qid for 3 days]. The neurological symptoms improved to some extent after each term. The steroid therapy had to be discontinued for 2 months between the second and third terms because of bacteremia.

During the first 2 months, the chimpanzee received intensive care with 24-h attention and continuous fluid therapy. Although he could drink water and eat fruits when put into the mouth, the food intake was not sufficient to support his nutritious requirements. He received iv fluid supplemented with amino acid, glucose (Aminofluid; Otsuka Pharmaceutical Co., Ltd.), and vitamins. One week after the onset, serum liver enzyme [aspartate aminotransferase (AST): 138 U/l, alanine aminotransferase (ALT): 466 U/l, gamma glutamyltransferase (GGT): 64 U/l] and ammonia (111 μg/dl) levels were elevated, possibly because of corticosteroid administration, but levels returned to normal range in 1 month following administration of glycyrrhizin (Stronger Neo-Minophagen® C; Minophagen Pharma. Co., Ltd., Tokyo, Japan), glutathione (Tathione; Astellas Pharma. Inc., Tokyo, Japan), and diisopropylamine dichloroacetate powder (Liverall; Daiichi-Sankyo Co., Ltd.). Three weeks after the onset, bacteremia was evident in the blood culture, which was subsequently monitored once a week. *Enterococcus faecalis* (*E. faecalis*), coagulase-negative *Staphylococci*, and *Klebsiella pneumoniae* (*K. pneumonia*) alternated in the results, and antibiotics were selected according to the sensitivity results. Selected antibiotics were administered intravenously for the first 2 months, intramuscularly for another 3 months as the fluid therapy was discontinued, then orally until blood culture was negative for three consecutive weeks.

The chimpanzee was anesthetized once or twice every week until 16 months, then once a month until 21 months after the onset for veterinary care and the cleaning of the chimpanzee's body and bedding. Initially, ketamine alone was used to induce anesthesia, but after 10 months, the combination of ketamine and butorphanol was used in an attempt to achieve better analgesic effects for pain presumably caused by the treatment of pressure ulcers. Isoflurane was used to maintain anesthesia.

While the chimpanzee was under anesthesia, the cage and bed were cleaned and improved, the animal's body was cleaned, the pressure ulcers were treated, blood samples were taken to monitor CBC, serum chemistry, and blood culture, and various medicines were administered, including glutathione, vitamin B12 derivative (Methycobal; Eisai Co., Ltd., Tokyo, Japan), vitamin C (C-Para; Takata Seiyaku Co., Ltd., Tokyo Japan), metoclopramide (Primperan; Astellas Pharma. Inc.), H2 blocker (Famotidine; Sawai Pharma. Co., Ltd., Osaka, Japan), and carprofen (Rimadyl; Pfizer Japan, Tokyo, Japan).

All pressure ulcers were cleaned with saline, bupivacain (Marcain 0.5%; AstraZeneca K. K.,Osaka, Japan) was applied to manage pain caused by the treatment, debridement of devitalized tissues and excessive granulation tissues from pressure ulcers was performed, and dressings (Plus moist; Zuiko Medical, Osaka, Japan) were applied with white petrolatum (White Vaseline; Kenei Pharmaceutical Co., Ltd., Osaka, Japan) or Intrasite Gel (Smith & Nephew KK, Tokyo, Japan) to keep the ulcer beds continuously moist. Finally, ulcers were covered with Opsite (Smith & Nephew KK). When the pressure ulcers on the knees and trochanteric area reached the articular cavities, the cavities were swabbed and cultured. The knee was positive for *Enterococcus* sp., *K. pneumonia*, *P. aeruginosa*, *S. aureus*, and *Candida* sp., and the trochanteric area was positive for *Bacillus* sp., *P. aeruginosa*, and *S. aureus* on day 210. Feeding tubes (8 Fr) were inserted, and articular cavities were thoroughly washed with saline. Selected antibiotics were applied inside the articulations based on sensitivity results.

Nutrition

The body weight of the chimpanzee dropped from 57 to 35 kg in the first 2 months, despite his ability to swallow some foods or water and continuous iv fluid therapies (Fig. 2). Starting at one and a half months, high-potency nutritious liquid was administered into the stomach when he was anesthetized and the intravenous fluid was discontinued. The high-potency nutritious liquid contained enteral hyperalimentation (Ensure H, 250 ml; Meiji Dairies Co., Tokyo), methycobal, potassium gluconate (Gluconsan K 4 mEq, 1 g; POLA-Pharma, Tokyo, Japan), vitamin B1 derivative, vitamin B6, and vitamin B12 (Vitamedin, 1 g; Daiichi-Sankyo Co., Ltd., Tokyo, Japan), multi-vitamin (Panvitan, 1 g; Takeda Pharmaceutical Co., Ltd., Osaka, Japan), resistance lactobacillus (Lacspan, 1 g; Kissei Pharmaceutical Co., Ltd., Tokyo, Japan), simethicone (Gascon, 1 g; Kissei Pharmaceutical Co., Ltd.), powdered supplement tabs (Fe tabs, amino acid

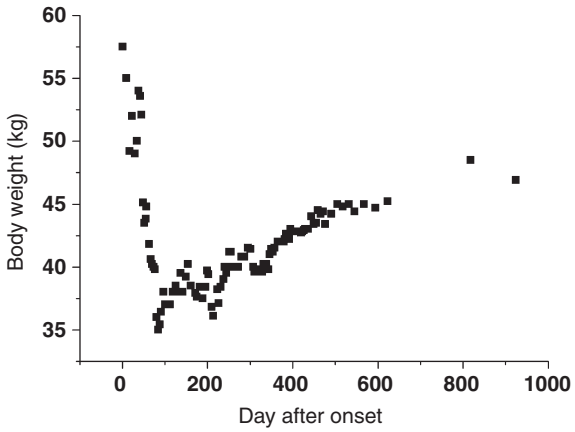

Fig. 2 Body weight (kg) of the chimpanzee.

tabs, multi-vitamin tabs, and spirulina), antibiotics depending on sensitivity tests, and one squashed banana. The animal was held upright for more than 10 minutes after the administration of the liquid nutrition to avoid regurgitation and aspiration. The chimpanzee was observed carefully during and following the recovery from anesthesia. No regurgitation or vomiting following the procedure was observed. Eventually, the chimpanzee regained his appetite, and his body weight slowly increased. Seven months later, even though the gastric administration ceased, his body weight continued to increase.

The serum potassium levels were slightly low at the onset (3.1 mEq/l) and continued to decline to 1.5 mEq/l on day 45 and stayed at 1.5–2 mEq/l, even though 40–80 mEq KCl/l was added to the fluid each time it was given. Two months after onset, 1 g of Gluconsan K was added to every 200 ml of drinking water, and the level of serum potassium gradually increased. The level of aldosterone was < 13 pg/ml.

General conditions and pressure ulcers

The initial signs of pressure ulcers on the dorsum along the spinous processes of the thoracic and lumbar vertebrae were noted on day 23 (Fig. 3A). At that time, it was not possible to reposition the chimpanzee frequently to prevent pressure ulcers because he was not cooperative about being turned. The chimpanzee was laid on an air mattress, and the structure of the bedding was constantly modified in an effort to relieve pressure on the dorsum and to prevent urine and feces from contacting the skin (Fig. 4A). His limbs were put in a sling to lessen the weight on the dorsum, and protective cushions were placed. However, pressure ulcers developed not only on the dorsum but also on the parts of the body in contact with the sling, i.e. the arms, legs, and knees. As the general condition of the chimpanzee declined and his bedridden status was protracted, pressure ulcers developed on the dorsum along the thoracic and lumbar vertebrae, in the scapular, lumbosacral, ischial, and trochanteric areas, and on the wing of the ilium (Fig. 3B) by 1 month after the onset. The ulcers on the knees and trochanteric area reached to the articulations by 3 months.

The bedding was changed from an air mattress to a mattress made of pressure-relieving material made for elderly dog care (Dog care mat; Takikoh Sewing, Aichi, Japan) at 189 days, and the chimpanzee was simply laid on the mattress from then on (Fig. 4B). By that time, he had begun to allow several caregivers to turn his body several times a day. His capacity for voluntary movement and condition of pressure ulcers gradually improved in the following months. He began to use his hands to eat fruits and supplementary tabs, and the pressure ulcers on his legs and knees continued to heal. At 8 months after the onset, the chimpanzee strongly objected to being turned and he lifted and repositioned himself using iron bars attached to his cage. At 9 months, the bed was improved so it could be tilted several times a day so that he could recline his upper body on the bed (Fig. 4C). His arms became strong enough to lift his whole body in the air at 10 months, and he began lifting himself and sitting on his buttocks.

After 11 months, the chimpanzee could maintain the sitting position for increasingly longer times and at greater frequency. His pressure ulcer improvement was proportional to the duration and incidence of his sitting position. The pressure ulcers on the acetabular margin were healed by 15 months after the onset. As he moved frequently, friction caused the ulcers on his lower dorsum and lumbosacral area to worsen temporarily. At 15 months, several removable partition bars were attached to the cage to divide the left and right sides of the cage. When the chimpanzee was in the left side of the cage, a caregiver could attach the bars and clean the right side of the cage, then remove the bars and ask the chimpanzee to move over to the right side while the left side was cleaned. This system improved the sanitary conditions inside the cage and the pressure ulcers on the dorsum of the chimpanzee. It also became possible to clean the dorsum around the pressure ulcers using a towel soaked in 0.05% chlorhexidine and warm water when he sat and turned his dorsum to the partition bars. By the time, the chimpanzee was remaining in a sitting position most of the day, and he started to fiddle with the pressure ulcer on the lower dorsum. At 16 months, it became possible

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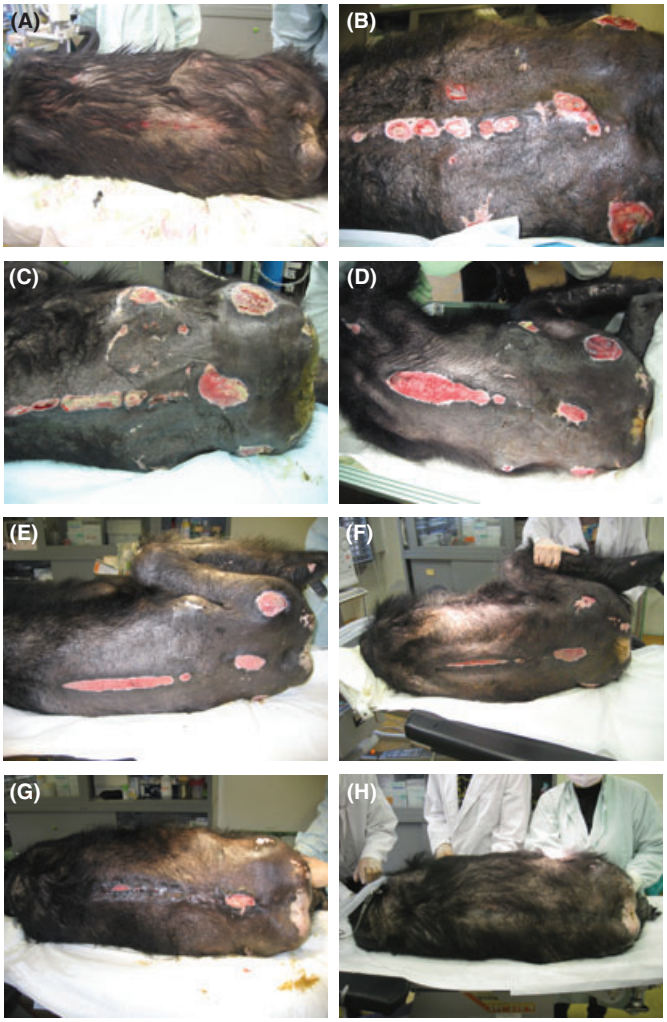

Fig. 3 Pressure ulcers on day 23 (A), day 88 (B), day 161 (C), day 248 (D), day 311 (E), day 420 (F), day 532 (G), day 925 (H).

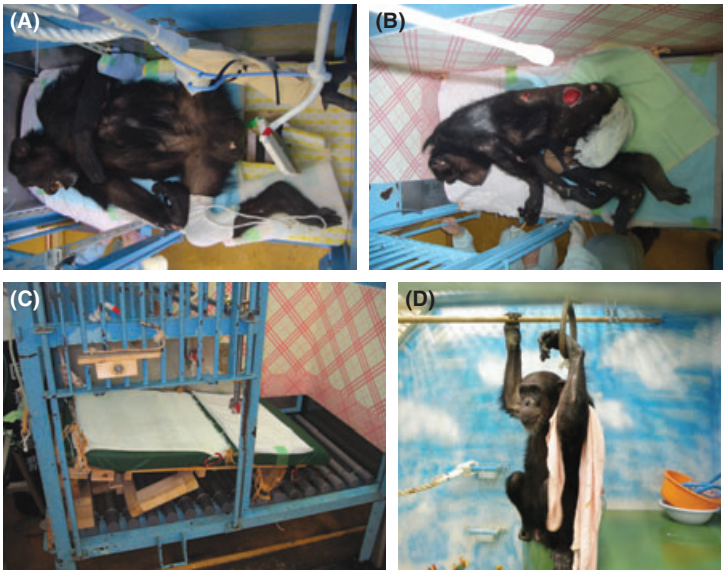

Fig. 4 The bedding and the condition of the chimpanzee on day 150 (A), day 189 (B), day 402 (C), day 988 (D). (A) The legs were on slings to relieve pressure on the dorsum. Urine and stools fell on the ground through the hole. (B) The chimpanzee was laid on the pressure-relieving mattress. (C) The bed could be tilted several times a day. (D) The chimpanzee in the new enclosure.

for caregivers to clean his body and treat pressure ulcers using silver sulfadiazine cream (Geben; Mitsubishi Tanabe Pharma Co., Osaka, Japan), aluminum hydroxy allantoinate (Isalopan; Aska Pharmaceutical. Co., Ltd., Tokyo, Japan), or a traditional formula, 'Bruns' solution,' containing iodoform, diethyl ether, camphor, and olive oil [13] without anesthesia.

Evaluation of the pressure ulcers

The pressure ulcers on the scapula, on the dorsum along the spinous process of the thoracic and lumbar vertebrae, in the lumbosacral and ischial areas, and on the wing of the ilium were Stage/Grade III according to the NPUAP/EPUAP system, which was a full-thickness skin loss involving damage or necroses of subcutaneous tissue that may extend down to, but not through, underlying fascia. Those on the knees and in the trochanteric areas which reached to the articulations were Stage/Grade IV, which was full-thickness wounds with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures.

Starting on day 301, the size of the pressure ulcers on the upper and lower dorsum and in the lumbosacral, right and left trochanteric areas were measured when the chimpanzee was under anesthesia for treatment and evaluated using the 'DESIGN' tool [11, 24]. The pressure ulcers in the scapular, ischial, iliac, knee, and trochanteric areas were healed by the time we attempted to assess them. DESIGN consists of six items used to assess severity of the wound; Depth, Exudate, Size, Infection, Granulation, and Necrosis. 'P' is added when a pocket is present. The size of the upper dorsum ulcer on day 311 (Fig. 3E) was 23×3 cm with a DESIGN rating of D3e1s5i1g1n0 = 11. The changes in size and DESIGN rating are shown in Fig. 5.

Rehabilitation

At onset, the flexor muscles were predominant over extensors in all limbs, which were contracted in the flexed position. After about 6 months, when both personnel and the chimpanzee became accustomed to interacting with each other, caregivers pulled his hands and feet to extend the arms and legs several times a day and massaged the hands and feet using warm towels. The sole of each foot was pushed, imitating finger-pressure therapy, and the toes were bent and extended. As the chimpanzee used his arms to lift his body up and move around in his cage, the arms were gradually stretched. The bedding was improved, and bars and ropes were attached in the cage to facilitate his movement. When the chimpanzee became strong enough to be dangerous to most of the caregivers, only a veterinarian (A. K.) and a keeper (S. W.) who had established good relationships with the chimpanzee were able to be in direct contact with him. They could extend his legs and arms as rehabilitation with less stress when they made 'laughing' sounds and the chimpanzee accepted to 'play'. On day 925, the chimpanzee was moved to a larger space especially renovated for him for further rehabilitation, where he could move around using his arms to hang on to ropes and bars. On day 988, although his legs were still in a flexed position, he could put some weight on his legs and move around on the floor using his legs (Fig. 4D).

Discussion

A chimpanzee developed acute onset of tetraparesis. The initial MRI showed a diffuse T2-weighted hyperintensive lesion, indicating either an inflammation or an infarction at the C1–2 level. Elevated CRP and neutrophils in the blood exams as well as increased protein levels in the CSF on the second day supported the presence of inflammation. There was no evidence of a compressive lesion, fracture, or traumatic injury. The chimpanzee had no history of irradiation. An autoimmune disease such as systemic lupus erythematosus (SLE) rarely presents as initial neuralgic symptoms. In this case, SLE was unlikely because of a negative result for antinuclear antibody and the course of disease. Alford and Satterfield [1] reported a case of paralytic illness resembling Guillain–Barre syndrome in a chimpanzee with a history of rabies vaccination and dental abscess, although the association of the history with the illness was uncertain. In their chimpanzee, the paresis progressed to flaccid symmetrical tetraplegia within 3 days, but by 1 week after onset, the chimpanzee could sit unaided again, and he could walk on all four limbs at 1 month. As regards this case, the course of the disease seemed to be different, and the chimpanzee had no history of vaccination or other noticeable signs of infectious disease before the onset of the disease.

Taken together, the condition of the chimpanzee in our case most resembled acute transverse myelitis (ATM), a focal inflammation of the spinal cord resulting in neural dysfunction in humans. Although it was not possible to perform precise neurological examinations, the signs and symptoms of the chimpanzee met most of the proposed diagnostic inclusion criteria in humans [28], which were (i) development of sensory, motor, or autonomic dysfunction attributable to the spinal cord, (ii) bilateral signs and/or symptoms, (iii)

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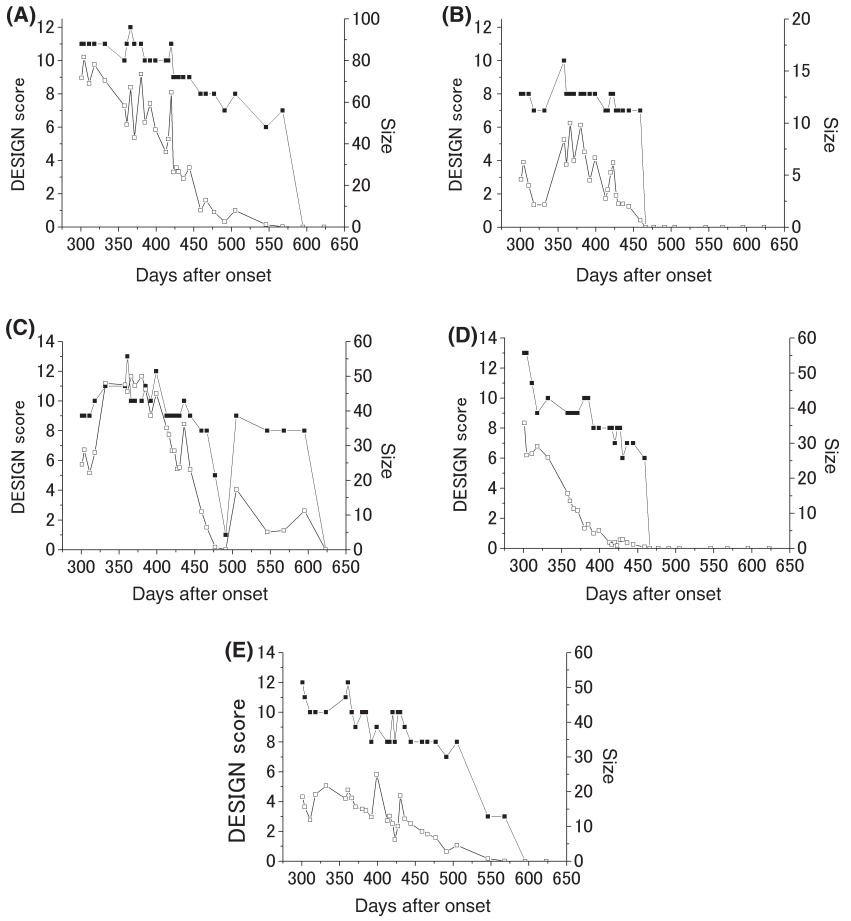

Fig. 5 Pressure ulcer size (□) and DESIGN scores (■) on upper dorsum (A), lower dorsum (B), and lumbosacral (C) areas, in left (D) and right (E) trochanteric areas.

clearly defined sensory level, (iv) exclusion of extra-axial compressive etiology by MRI, (v) inflammation within the spinal cord demonstrated by CSF, and (vi) progression to nadir between 4 hours and 21 days following the onset of symptoms. None of the proposed exclusion criteria was met; no history of previous radiation to the spine, no evidence of thrombosis of the anterior spinal artery or arteriovenous malformation, no serologic or clinical evidence of connective tissue disease, and no clinical sign of multiple sclerosis (MS) or optic neuritis. The brain and cranial nerves appeared to be intact throughout the 2-year course of the disease. The brain MRI was not taken, because of the lack of clinical indication, and the median sagittal brain image taken during cervical MRI did not show any multifocal lesion suggestive of MS (Fig. 1).

ATM can also be associated with various infectious agents including enterovirus, coxsackie virus [18, 25], CMV [22], echovirus [29], Epstein–Barr virus, herpes simplex virus, mumps virus, and VZV [28]. The serum antibodies were negative for these viruses except for CMV and VZV, and the antibody titers of CMV and VZV were not significantly elevated. Other typical symptoms of VZV were not evident in the chimpanzee, and the results were also positive in other chimpanzees in the institute, which indicated that VZV had been spread among the group in the past. While some cases of encephalitis caused by VZV without other typical symptoms in humans with immune deficiency have been reported [19], there was no evidence that the chimpanzee had an impaired immune system. The causes of ATM are sometimes uncertain and may be idiopathic in humans.

An established medical treatment does not exist for idiopathic ATM in humans. When viral causes are suspected, antiviral agents such as acyclovir, gancyclovir, and valganciclovir can be used [22, 29]. Steroid treatment has reported to be effective in some patients [14, 18, 22, 25, 29]. In this case, pulsed treatment with high-dose dexamethasone was attempted three times, and the motor function in all four limbs appeared to improve each time. However, bacteremia made it impossible to continue the steroid therapy for 2 months after the second round of therapy.

Hypokalemia, possibly because of malnutrition, might also have contributed to the deterioration of the

muscle function in the limbs, resulting in the delay of recovery. Anecdotally, the level of potassium tends to be lower in chimpanzees than in humans, and it can easily drop when the general conditions decline in chimpanzees (Udono, personal communication). Excessive secretion of aldosterone can cause hypokalemia, but in this case, the level of aldosterone was rather decreased. Although potassium chloride was added to the intravenous fluid, the level of serum potassium did not improve much. In contrast, when potassium gluconate was added to the drinking water, the level gradually increased, which coincided with improved food intake. Gastric feeding of high-potency nutritious liquid under anesthesia seemed to promote the chimpanzee's digestive function and triggered his appetite. The benefit exceeded the risks of regurgitation and aspiration since the procedure was performed carefully.

In the pathogenesis of pressure ulcers, the main factors implicated are interface pressure, shear, friction, and moisture [5, 10]. The major risk factors for the development of pressure ulcers in patients with SCI include immobility and inability to reposition the body, fecal and urinary incontinence, which increase moisture around the area, and poor nutritional status [10]. The principles of treatment for pressure ulcers include assessing severity, reducing pressure, frequent repositioning, cleaning of the skin, debridement, dressing, pain management, infection management, and proper nutrition [26]. In this case, the chimpanzee was clearly at risk with multiple factors, including inability to reposition and malnutrition. The pressure ulcers were only cleaned and treated when the chimpanzee was anesthetized twice a week, and this was also the only time the cage and bedding could be cleaned. The structure of the bedding prevented the urine and feces from contacting the skin, but the environment was not sufficiently clean. Infection management was difficult, and the blood culture was positive for several bacteria, including *E. faecalis* and coagulase-negative staphylococci, which have been reported to be the most common resident bacterial species found in persisting venous leg ulcers [8]. It is likely that the bacteremia was caused by the pressure ulcers, despite continuous use of antibiotics selected according to the sensitivity tests. The results of the bacterial culture from the articular cavity on the knees and trochanteric area were in part consistent with the results from blood culture. It has been reported that antibiotic treatment is not always successful in chronic wounds, at least partly because of the ability of colonizing bacteria to establish a biofilm and proliferate within it [2]. Several cases of bacteremia because of pressure ulcers have been reported [12]. In this case, bacteremia did not persist and the problem subsided as the condition of the pressure ulcers improved.

The standard four-stage/grade classification systems developed by NPUAP and EPUAP are reliable and convenient, but they are not suitable for 'reverse staging', because healing from Stage IV does not progress through Stage III to Stage I but rather occurs by contraction and scar tissue formation [26]. The 'DESIGN' tool [24] recommended by JSPU was developed to evaluate especially the healing process of pressure ulcers and successfully used to evaluate pressure ulcer healing after liver transplantation in two patients [11]. In this case, the sizes of the pressure ulcers on the upper dorsum, lower dorsum, lumbosacral, and right and left trochanteric area were measured, and assessments using the DESIGN tool were attempted. The size of the ulcers gradually decreased in the course of 6 months (around days 300–480), except that, as the chimpanzee moved, friction caused the ulcers on his lower back and lumbosacral area to worsen temporarily. In contrast, the severity of the pressure ulcers assessed using the DESIGN tool changed more slowly until the last several weeks before the final healing, when the score dropped steeply. Although the treatments successfully prevented progression, they did not promote epithelization. The granulation tissues appeared to be good, but healing did not progress to epithelization for more than 1 year, which may reflect the relatively stable phase in the DESIGN rating. Considering that deep puncture wounds or deeply incised wounds had been observed to heal in several weeks or 1 month in wild chimpanzees [9], the healing time of the pressure ulcers in this case was remarkably long even after when the chimpanzee was able to sit up. It is also reported in human patients that a wound may 'look good' and nevertheless fail to contract, epithelialize, or close in a timely manner [3]. It can be extremely difficult for pressure ulcers to heal. In humans, healing rates for Stage III pressure ulcers may be as high as 59% at 6 months, but other patients require up to 1 year of therapy [26].

The importance of training to cooperate with husbandry and research procedures in captive non-human primates has been well recognized among researchers and caretakers in zoos and research facilities [4, 15, 20]. In our institute, the training of chimpanzees to present various parts of the body, for physical examination, venipuncture and intramuscular injection has been successful in some chimpanzees. However, the characteristics of the chimpanzee in this case made it difficult for such training before the onset of the disease. After the onset, the chimpanzee received various types of care every day and gradually accepted the

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presence of caregivers. After 6 months, when the chimpanzee started to accept repositioning, his general condition, mobility, and pressure ulcers on the limbs synchronously improved. When the chimpanzee spent most of his time sitting, he started to touch the ulcer on the lumbosacral area, causing the ulcer to worsen. Caregivers also started to observe coprophagia, an abnormal behavior in which the chimpanzee would eat his feces and touch the ulcer using the same finger. Duncan and Levi [6] reported that a major obstacle to sore closure in cynomolgus macaques was a tendency for the animals to scratch the area with their fingernails. They suggested that environmental enrichment provided mental stimulation for the animals and may have lessened their scratching at the sores. In this case, we provided various toys and a touch screen monitor that showed pictures of chimpanzees in the institute or in the wild. Ropes and bars were attached to the cage so that he could move around inside the cage. Various caregivers visited the chimpanzee each day and interacted with him. By this time, several caregivers were able to have direct contact with the chimpanzee and treat the ulcer without anesthesia. The daily cleaning and treatment of pressure ulcers may have promoted their final healing. Cooperation of the chimpanzee during repositioning and treatment, removal of the pressure, nutritional supplementation, the proper medical treatment, and patience on the part of the staff were all required for the successful healing of the pressure ulcers.

The chimpanzee was in severe incapacitated neurological condition with bedridden status and required 24-hour attention for 2 months followed by special care for over a year. Although the chimpanzee's condition was deteriorating and the situation was extremely difficult for caregivers as well as the chimpanzee, especially in the first 2 months, the option of euthanasia was not chosen because he was fully alert. It was fortunate that the essential functions such as breathing, swallowing, micturition, and defecation were intact. The condition of the chimpanzee was much better than that of some surviving human patients. The relationship between the chimpanzee and his caregivers changed over the course of long-term care. Although the chimpanzee was difficult to control initially, the development of relationships of mutual trust with several caregivers was essential for quality care, including repositioning, pressure ulcer therapy, and rehabilitation.

Acknowledgments

We thank Drs Takashi Kageyama, Kiyoaki Matsubayashi, and Hirohisa Hirai for their support of this case. We thank all staff members and students who took care of the chimpanzee: Tomomi Ochiai, Gaku Ohashi, Tomoko Imura, Toyomi Matsuno, Shinya Yamamoto, Laura Martinez, Yoshiaki Sato, Takaaki Kaneko, Fumihiro Kano, Sana Inoue, Suzuka Hori, Tomoko Takashima, Etsuko Nogami, Kazue Haguri, Seiji Hayakawa, Christopher Martin, Ikuma Adachi, Yuko Hattori, Yumi Yamanashi, Hanako Sasaki, and Yasushi Furuhashi. We thank Drs Akimitsu Mikami, Takao Oishi, Takeshi Nishimura, Keiji Ono, and Tomoko Sakai for performing the MRI scanning. We thank Drs Reina Fujiwara, Satoru Matsunaga, and Ryohei Nishimura from the Veterinary Medical Center, University of Tokyo, and Dr Akio Suzumura at the Research Institute of Environmental Medicine, Nagoya University, for their assistance in interpreting the MRI images. Thank you to Drs Toshifumi Udono, Michiko Fujisawa, and Naruki Morimura at Chimpanzee Sanctuary Uto and Dr Shunji Goto at Amami Wild Animal Research, Inc., for providing valuable information on veterinary care of chimpanzees. We thank Dr Naoki Koriyama for serological investigation. Thank you to Dr Vjekoslav Miletic for critical reading of the manuscript and valuable advice. This study was financially supported by the following grants: MEXT 16002001, 20002001 to TM, and JSPS-gCOE (A06).

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