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Reversible MR Changes in the Cat Brain after Cerebral Fat Embolism Induced by Triolein Emulsion

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BACKGROUND AND PURPOSE: **Clinical cerebral-fat embolism shows both reversible and irreversible changes. We used MR imaging to investigate the reversibility of embolized lesions induced with a fat-emulsion technique and to evaluate the histologic findings.**

METHODS: **A fat emulsion was made with 0.05 mL of triolein and 20 mL of normal saline and vigorous to-and-fro movement through a three-way stopcock. In 50 cats, the internal carotid artery was infused with the fat emulsion. Cats were divided into six groups on the basis of time delay after embolization: 1 hour; 1 and 4 days; and 1, 2, and 3 weeks. MR imaging and histologic examination were performed at these times.**

RESULTS: **Embolized lesions were hyperintense on T2-weighted images, isointense or mildly hyperintense on diffusion-weighted images, isointense on apparent diffusion coefficient maps, and enhancing on gadolinium-enhanced T1-weighted images at 1 hour. These MR imaging findings were less evident at day 1 and reverted to normal after day 4 (isointense on all images). Electron microscopy showed minimal findings in the cortical lesion in groups 1 and 2 (group 1 at 1 hour and group 2 at 1 hour and 1 day). Light microscopic findings revealed evidence of necrosis—small focal gliosis and demyelination in the periventricular white matter—in only one cat. The number of intravascular fat globules was not significantly different between groups, as visualized by oil red O staining.**

CONCLUSION: **Cerebral-fat embolism induced by a triolein emulsion revealed reversible MR findings and minimal histologic findings.**

MR imaging findings of cerebral-fat embolisms include multifocal hyperintensities in the gray matter and white matter of cerebrum, cerebellum, and brain stem on T2-weighted images (T2WIs) in the acute or subacute stage; these lesions are mostly reversible (1–3). In experimentally induced cerebral-fat embolism (with a single-bolus injection of fat) (4, 5), there are two types of the embolized lesions, with the type showing vasogenic edema in the hyperacute stage reverting to a normal appearance in the subacute stage.

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We hypothesized that the type of lesion and its reversibility depends on the size of fat globules. This study was conducted to investigate whether embolized lesions induced with a fat-emulsion technique (to make small fat globules) are reversible MR findings and to evaluate the histologic findings over time. To our knowledge, this is the first study of its type.

Methods

Animal Models and Embolization with a Fat Emulsion

The Animal Research Committee of the Medical Research Institution approved all experiments and surgical procedures. A total of 55 adult cats of both sexes weighing 2.5–3.5 kg were anesthetized with intramuscularly administered ketamine HCl (2.5 mg/kg; Korea United Pharm, Seoul, South Korea) and xylazine (0.125 mg/kg; Bayer Korea, Seoul, South Korea) and ventilated with room air. Body temperature was measured with a rectal probe (MGA-III 219; Shibaura Electronics, Tokyo, Japan) and maintained at 35.5°C–36.5°C. Respiration rates were checked before, during, and after the procedure. Catheters were placed in the left femoral artery to allow for monitoring of blood pressure and blood gas levels and in the left femoral vein for the injection of a contrast material or drugs. Either common carotid artery was selected via the transfemoral

approach with a 3.0F microcatheter (MicroFerret-18 infusion catheter; William Cook Europe, Bjaeverskov, Denmark). The tip of the microcatheter was positioned just proximal to the entrance of the intracranial portion of the internal carotid artery under fluoroscopic guidance.

A 1-mL syringe containing 0.1 mL of neutral triglyceride triolein (1,2,3-tri[cis-9-octadecenoyl]glycerol, 99% purity, d = 0.91 g/mL; Sigma, St. Louis, MO) and a 25-mL syringe containing 20 mL of saline were connected to a three-way stopcock. The fat emulsion was made by mixing the three-way stopcock with vigorous to-and-fro movement of the syringes for 2 minutes. The emulsified fat was infused cephalad to the internal carotid artery at a rate of 4 mL/seconds for 5 minutes.

MR Imaging

Cats were randomly assigned to one of six experimental groups. MR imaging (1.5-T MR unit; Sonata, Siemens, Erlangen, Germany) was commenced 1 hour after embolization, followed by further imaging after 1 and 4 days and at 1, 2, and 3 weeks as follows: group 1 at 1 hour; group 2 at 1 hour and 1 day; group 3 at 1 hour and 1 and 4 days; group 4 at 1 hour, 1 and 4 days, and 1 week; group 5 at 1 hour, 1 and 4 days, and 1 and 2 weeks; and group 6 at 1 hour, 1 and 4 days, and 1, 2, and 3 weeks. Cats were placed in a prone position within a pediatric MR positioner, and a flexible coil was placed above the head. Images were acquired in the coronal plane. For spin-echo imaging, the following imaging parameters were used: TR/TE of 3000/96 for T2WIs and 320/20 ms for T1-weighted images (T1WIs), section thickness of 4 mm with a 0.1-mm gap, FOV of 70–75 mm, two excitations, and an acquisition matrix of 210 × 256. Diffusion-weighted images (DWIs) were obtained by using an echo-planar sequence. The imaging parameters were as follows: FOV of 130 mm, 128 phase-encoding steps, section thickness of 4 mm, gap of 0.1 mm, and acquisition matrix of 96 × 160. The diffusion sensitizing gradient was oriented in the three axes with b values of 0 and 1000 s/mm^2. Apparent diffusion coefficient (ADC) maps were obtained at the same time. For contrast-enhanced studies, 0.2 mmol/kg gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) was injected intravenously.

The time course of the signal intensity and abnormal enhancement due to the lesion was evaluated visually. The lesion site was examined and tabulated as ipsilateral or contralateral hemisphere and deep gray matter.

Histologic Examination

The brain was removed from the cranium immediately after the cats were sacrificed with an intravenous injection of sodium thiopental. A homemade cutting device was used to dissect the brains into 4-mm-thick sections in the same coronal plane as that of the MR images.

For electron microscopy, three areas of the gray matter correlating to lesions observed on the MR images and another three areas of normal contralateral hemisphere were selected. These areas were cut into 1-mm cubes for the preparation of electron microscopy blocks. Samples were examined with a transmission electron microscope (JEM 1200 EX-II; Jeol, Tokyo, Japan) according to the method of Kim et al (4). The presence of intravascular or extravascular fat globules, the integrity of the capillary endothelial wall, widening of the perivascular interstitial space, and neuronal swelling were evaluated.

Three sections of the brain correlating to lesions observed on the MR images and normal contralateral hemisphere were selected for light-microscope examinations with Luxol fast blue, hematoxylin-eosin, and oil red O stains. Demyelination of the white matter was examined by using Luxol fast blue stain. Necrosis and gliosis were evaluated on hematoxylin-eosin stains.

For semiquantification of fat globules, oil red O staining was performed in brain tissues from all six experimental groups. In cases showing fat globules, the globules were detected as a distinctive pinkish-red staining. Irrespective of size, only well-defined round spaces associated with pinkish-red fat were counted (Fig 1B). Round spaces not associated with pinkish-red fat material were excluded from the appraisal. First, each slide was overviewed by using a microscope (BX50; Olympus Optical, Tokyo, Japan) under 40× magnification (about 23.75 mm^2 per field), and 10 areas showing an increased density of fat globules were selected. In each area, fat globules were counted under 200× magnification (about 0.95 mm^2 per field). The final fat-globule frequency was calculated as the average value of pinkish-red fat globules per square millimeter. Two independent observers (H.J.K., C.H.L.) examined all slides; interobserver variability was minimal ($P < .05$, χ^2 test). Statistical analysis of between-group differences in the number of fat globules was performed by using a nonparametric Kruskal-Wallis test with the SPSS package of computer programs for Windows, version 10.0.7, 2000 (SPSS Inc, Chicago, IL). A P value less than .05 was regarded as indicating a statistically significant difference.

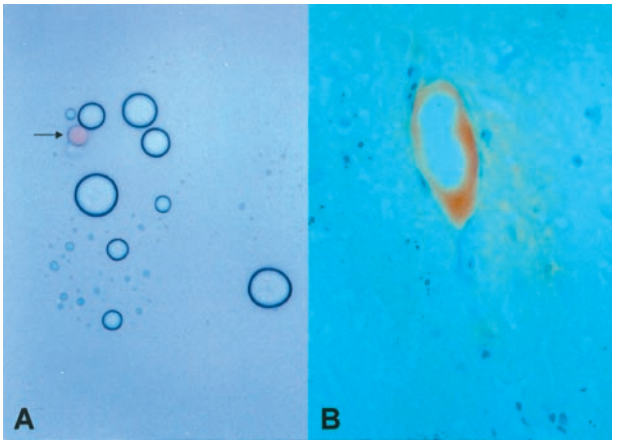

FIG 1. Fat globules.
A, Photomicrograph of the fat emulsion. The fat globules are of variable size, mostly less than two times the size of red blood cells (*arrow*, original magnification ×40).
B, An intravascular fat globule is pinkish-red on oil red O staining (original magnification ×200).

Results

The size of fat globules in the emulsion was compared with that of red blood cells under light microscopy (Fig 1A). The fat globules ranged from 1 to 30 μm; most were less than two or three times larger than red blood cells.

Of the 55 cats initially included in the study, five died during the protocol; hence, the data from 50 cats were analyzed. Seven cats were studied in each group except for group 4, which comprised 15 cats. T1WIs, T2WIs, and gadolinium-enhanced T1WIs were obtained in each cat (Table 1). DWIs and ADC map were additionally performed in group 4.

MR Imaging Findings at 1 Hour

MR images were obtained in all 50 cats of the six groups at 1 hour after embolization. Most of the lesions were located in the superficial gray matter. On T1WIs the lesions were isointense (39 cats, 78%) or slightly hypointense (11 cats, 22%). On T2WIs the lesions were hyperintense in 27 cats (54%) (Fig 2, *A1*). Gadolinium (Gd)-enhanced T1WIs revealed le-

TABLE 1: MR imaging results in cats as a function of time after embolization

Imaging*	Hyperintensity	Isointensity	Hypointensity
1 h (n = 50)			
T1WI	0	39	11
T2WI	27	23	0
DWI	3	12	0
ADC	0	15	0
1 d (n = 43)			
T1WI	0	33	10
T2WI	12	31	0
DWI	0	15	0
ADC	1	14	0
4 d (n = 36)			
T1WI	0	34	2
T2WI	1	35	0
DWI	0	15	0
ADC	0	15	0
1 wk, (n = 29)			
T1WI	0	29	0
T2WI	0	29	0
DWI	0	15	0
ADC	0	15	0
2 wk (n = 14)			
T1WI	0	14	0
T2WI	0	15	0
3 wk (n = 7)			
T1WI	0	7	0
T2WI	0	7	0

Note.—Enhancement on Gd-enhanced T1WIs was as follows: at 1 hour, n = 44; at 1 day, n = 12; at 4 days, n = 1; and at 1, 2, and 3 weeks, n = 0.

* DWI and ADC in group 4 cats (n = 15).

sional enhancement in 44 cats (88%) (Fig 2, *B1*). On DWIs of the 15 cats of group 4, the lesions were isointense in 12 cats (80%) and slightly hyperintense in three cats (Fig 2, *C1*). The ADC maps for group 4 all exhibited isointensity (Fig 2, *D1*).

The subcortical white matter exhibited hyperintensity on T2WIs in 11 cats and contrast enhancement in 18 cats. However, the subcortical lesions were not extensive. In 24 cats, lesions were present in the ipsilateral deep gray matter. These lesions were also slightly hyperintense or isointense on T2WIs, and enhanced on Gd-enhanced T1WIs. The contralateral hemisphere contained no abnormalities.

MR Imaging Findings at Day 1

MR images were obtained in 43 cats of groups 2–6 at 1 day after embolization. The lesions were slightly hypointense in 10 cats on T1WIs. T2WI hyperintensity was decreased (Fig 2, *A2*), and it was evident in 12 cats, 10 of which exhibited hyperintense lesions in the white matter. Twelve cats exhibited contrast enhancement, but this was lower in both degree and size compared with that at 1 hour (Fig 2, *B2*). The lesions in deep gray matter appeared as mild hyperintensities on T2WIs in eight cats, and as mild enhancement on Gd-enhanced T1WIs in four cats. On DWIs in all 15 cats of group 4, the lesions were all isointense (Fig 2, *C2*). On the ADC maps, one cat showed mild hyperintensity in the white matter, and other cats exhibited isointensity (Fig 2, *D2*).

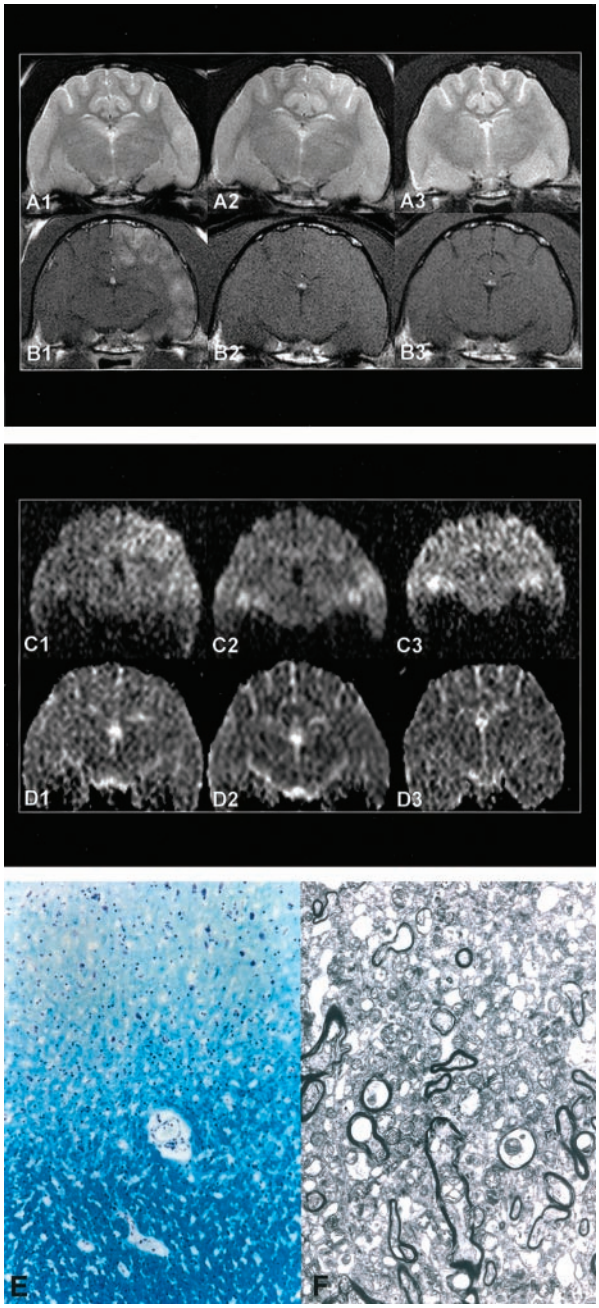

FIG 2. Images obtained in a cat in group 4: *A* indicates T2WIs; *B,* Gd-enhanced T1WIs; *C,* DWIs; *D,* ADC maps; *E*, light photomicrograph; *F*, electron photomicrograph. *1* indicates 1 hour after embolization; *2*, 1 day; and *3*, 7 days. At 1 hour, the embolized lesion in the left hemisphere appears hyperintense in *A1*, enhanced in *B1*, mildly hyperintense in *C1*, and isointense in *D1*. At 1 day, T2WI hyperintensity (*A2*) and contrast enhancement (*B2*) are substantially decreased and not evident at day 7 (*A3*, *B3*). After day 1, DWIs (*C2, C3*) and ADC maps (*D2, D3*) reveal isointensity of the lesion. In *E*, Light microscopy of the gray matter (*top*) and white matter (*bottom*) shows no evidence of demyelination (Luxol fast blue stain, original magnification ×100). In *F*, Electron microscopy of the gray matter shows no evidence of neuropil or interstitial swelling (original magnification ×3000).

TABLE 2: Electron microscopic findings in cats in groups 1–6

Group	Intravascular Fat Globule	Defect in Blood-Brain Barrier	Perivascular Interstitial Swelling	Neuronal Swelling
1 (n = 7)	7	6	4	3
2 (n = 7)	7	5	5	7
3 (n = 7)	7	3	2	1
4 (n = 15)	12	9	2	5
5 (n = 7)	6	2	2	2
6 (n = 7)	6	1	0	0
Total (n = 50)	45	26	15	18

MR Imaging Findings at Day 4

MR images were obtained in 36 cats of groups 3–6 at 4 days after embolization. T1WIs had slight hypointensities in only two cats. Thirty-five cats (97%) showed isointensity on T2WIs and no contrast enhancement. Only one cat showed mild T2WI hyperintensity and mild contrast enhancement on a Gd-enhanced T1WI. The 15 cats of group 4 all exhibited isointensity on DWIs and ADC maps. The deep gray matter lesions also all appeared as isointensities on T1WIs and T2WIs without contrast enhancement.

MR Imaging Findings at Weeks 1–3

MR images were obtained in 29 cats at 1 week (groups 4–6), 14 cats at 2 weeks (groups 5 and 6), and seven cats at 3 weeks (group 6) after embolization. The embolized lesions all appeared as isointensities on T1WIs and T2WIs (Fig 2, *A3*), with no contrast enhancement on Gd-enhanced T1WIs at these times (Fig 2, *B3*). The cats of group 4 had also isointensities on DWIs and the ADC maps (Fig 2, *C3* and *D3*).

Histologic Findings

Brain tissues were obtained from the lesion and from the contralateral normal hemisphere in all 50 cats. On electron microscopy, most portions of the gray matter of the embolized hemisphere showed minimal changes relative to the normal contralateral side (Table 2). Intravascular fat globules were seen sporadically in 45 cats. Four cats exhibited phagocytosed or intramural fat globules (with a size of less than 2.5 μm) rather than intravascular ones. The mean size of the intravascular fat globules was 14.3 μm (range 4–42 μm). Defects of the endothelial wall of capillaries containing fat globules were seen in 26 cats (six cats in group 1, five in group 2, three in group 3, nine in group 4, two in group 5, and one in group 6). However, the defect was focal and not frequent in each field. In 21 of 47 cats showing intravascular fat globules, this defect was not evident.

Perivascular interstitial swelling was seen in 15 cats (four cats in group 1, five in group 2, two in group 3, two in group 4, two in group 5, and none in group 6). However, the swelling was mild—less than 5 μm of the longest diameter of the interstitium in 14 cats. Only one cat of group 4 showed moderate swelling of the interstitium (but still less than 10 μm) in one electron microscopic field.

TABLE 3: Intravascular fat globules in cats in groups 1–6

Group	Mean Number per mm^2*	Mean Rank†
1 (n = 7)	3.62	25.25
2 (n = 7)	1.45	14.92
3 (n = 7)	4.46	23.33
4 (n = 15)	5.62	27.71
5 (n = 7)	4.17	22.75
6 (n = 7)	2.11	18.50

* Intravascular fat globules were determined by means of oil red O staining.

† P = .397, Kruskal-Wallis test.

Neuropil swelling was seen in 18 cats (three cats in group 1, seven in group 2, one in group 3, five in group 4, two in group 5, and none in group 6). Only two cats of group 2 and one cat of group 4 showed moderate neuronal swelling (less than 10 μm of the longest diameter of the cell), and in others this was mild (less than 5 μm). Also, the neuropil swelling was not frequent in each field.

On light microscopy, most examination areas in all cats had a normal appearance (Fig 2, *E*). However, one cat of group 4 exhibited small necrosis and gliosis in hematoxylin-eosin staining and focal demyelination in Luxol fast blue staining in the periventricular white matter. Intravascular fat globules were seen sporadically in the gray and white matter in oil red O staining (Fig 1B). A semiquantitative analysis of the number of fat globules, however, revealed no significant difference between groups (P = .397) (Table 3).

Discussion

The major finding in the present study is that embolized lesions induced with a fat-emulsion technique showed reversibility on follow-up MR images. In the hyperacute stage, the lesions appeared as isointensities or slight hyperintensities on T2WIs and DWIs and as isointensities on the ADC map images. Most of the embolized lesions were type 2, according to Kim et al (4, 6), and represent the occurrence of vasogenic edema within the lesions. The lesions were also associated with blood-brain barrier disruption resulting in lesional enhancement on Gd-enhanced T1WIs. In the acute stage (day 1), however, the T2WI hyperintensity and contrast enhancement of lesions were markedly decreased. After day 4, all the lesions reverted to a normal appearance on MR images.

Lipophilic agents can penetrate the lipid mem-

brane by diffusion (7). However, the pathogenesis of disruption of the blood-brain barrier by fat is still unclear. To date, tissue damage is believed to be the result of a combination of mechanical and biochemical effects of fat (8–11). The biochemical theory assumes that intravascular fat results from lipid mobilization from depot sources, or loss of chylomicron emulsion stability, resulting in coalescence and formation of fat globules. The driving force for these initial biochemical changes is trauma-induced catecholamine release. Fat embolized in the lung is converted to free fatty acids by the action of local pulmonary lipases. Free fatty acids are toxic to the lung and disrupt capillary epithelial function, leading to edema, hemorrhage, and atelectasis. The local inflammatory and toxic reactions are responsible for the delayed and dramatic respiratory distress seen in fat embolism, and are probably the cause of fever. The release of thromboplastin that occurs with orthopedic trauma induces platelet aggregation onto abnormal surfaces and accelerates the coagulation cascade. This latter process may be the mechanism responsible for the diffuse systemic and CNS microvascular thrombosis and petechiae seen in fat embolism (11). Clinical and experimental cerebral-fat embolisms demonstrate ischemic infarction due to vascular occlusion and also vasogenic edema due to reversible changes (1–3, 5, 6). We realized that the size of fat globules could be an important factor in determining the types and reversibility of the embolized lesions. Therefore, the present study used the technique of emulsion to produce fat emboli that were considered too small to cause mechanical vascular obstruction, and thus a biochemical reaction is more likely to be the underlying mechanism for the results obtained. This result could be applicable to the study of disruptions to the blood-brain barrier induced with fat.

There is a growing list of endogenous chemicals that can open the blood-brain barrier. This suggests that in inflammatory states, and probably also in normal physiologic conditions, opening of the blood-brain barrier induced by naturally occurring mediators may serve a useful function and may be well tolerated by the brain. If the blood-brain barrier is regarded as an endothelium that can be modulated without dangerous sequelae, deliberate blood-brain barrier opening could be considered a justified therapeutic strategy for some CNS disorders (7, 12–15). Most clinical experience with blood-brain barrier opening has come from osmotic opening, in which an intracarotid arterial injection of 25% mannitol is used to cause endothelial cell shrinkage and the opening of tight junctions for a period of a few hours (16). Chemical opening is a potentially more controllable and selective process. Clinical trials with the bradykinin analog RMP7 have been based on animal studies in which intracarotid arterial administration of bradykinin caused a transient increase in the permeability of tumor capillaries without affecting the permeability of normal capillaries (17). The leukotriene LTC4 has also been shown to selectively open the blood-brain barrier in the region of tumors in animal experiments (18). Triolein emulsion is a type of chemical opening of the blood-brain barrier, and the present study showed that its effects appear to last from several hours to a maximum of 3 days. Further investigations should assess neurologic adverse effects and the benefits of barrier opening induced by triolein emulsions.

One cat showed a small focal gliosis and demyelination at the periventricular white matter on histologic examination. A limitation of the present study is that the emulsion was made manually, and thus the fat globules were of variable sizes (Fig 1A). Ischemic infarction in the cat might have resulted from a large globule, but MR imaging of this cat revealed no evidence of infarction at the same area (the lesion may have been too small for detection by MR imaging).

Electron microscopy revealed similar findings in the lesion and contralateral normal hemispheres in most fields (Fig 2F). However, fat globules, minimal neuropil swelling, or perivascular interstitial widening was seen sporadically in the lesion side, especially in groups 1 and 2. This incidence of abnormal findings tended to decrease from group 3 to group 6. However, disruptions of the endothelial wall were few and there was no remarkable difference between each group. Therefore, the contrast enhancement and T2WI hyperintensity observed were probably due to the effect of fat on the endothelial wall rather than to endothelial defects.

In the present study, cats were divided into six groups according to time delay after embolization to evaluate any histologic differences over the natural course. Groups 1 and 2 showed more (mild) neuronal or perivascular swelling than other groups on electron microscopy. Intravascular fat globules were seen sporadically in the gray and white matter, but there was no statistical difference in the number of the fat globules between groups when using oil red O stain. This result suggests that microvascular occlusion by fat globules was independent of time after embolization in the present study.

Conclusion

Cerebral-fat embolism induced by triolein emulsion revealed T2 hyperintensity, isointensities or mild hyperintensities on DWIs, isointensities on ADC maps, and contrast enhancements on Gd-enhanced T1WIs at 1 hour. These MR imaging findings were less evident at day 1 and reverted to isointensities after day 4 on all images. Electron microscopy showed mostly normal findings except mild perivascular or neuropil swelling in the cortical lesion at 1 hour and day 1. Light microscopic findings revealed evidence of necrosis in only one cat in the periventricular white matter. The number of intravascular fat globules was not significantly different between each group. This result may be useful in future studies of the blood-brain barrier affected by the fat-emulsion technique.

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Errata

The authors and their affiliations are incorrectly listed in the article **Reversible MR Changes in the Cat Brain after Cerebral Fat Embolism Induced by Triolein Emulsion**, AJNR 25:958–963, June/July 2004. The authors and their respective affiliations should be listed as:

Hak J. Kim, Chang H. Lee, Hae G. Kim, Sang D. Lee, Suk M. Son, Yong W. Kim, Choong K. Eun and Seung M. Kim

From Pusan National University College of Medicine, Pusan National University Hospital, Department of Radiology (H.J.K.), Department of Pathology (C.H.L.), Department of Anesthesiology (H.G.K.), Department of Urology (S.D.L.), and Department of Internal Medicine (S.M.S.), Pusan, South Korea and Inje University College of Medicine, Department of Radiology (Y.W.K., C.K.E., S.M.K.), Pusan, South Korea.

The authors of the same article would also like to acknowledge an error, which occurs, in the first paragraph on page 959. The last sentence of the paragraph should read "The emulsified fat was infused cephalad to the internal carotid artery at a rate of 4mL/minutes for 5 minutes."

MR Imaging of the Temporal Stem: Anatomic Dissection Tractography of the Uncinate Fasciculus, Inferior Occipitofrontal Fasciculus, and Meyer's Loop of the Optic Radiation, AJNR 25:677–691, 2004

Addendum:

As a point of clarification, only the lateral surfaces of the tracts were exposed by dissection (2). The color coded fasciculi in the specimen photographs, 3D MR renderings, and cross sectional MR images, show only the lateral surface and not the entire thickness of the tracts.

Please note that (2) refers to reference #2 in the article.