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Results of Acute Cerebral Anoxia in Adults: is it a Reversal Sign?

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Abstract: Objective: The aim of this study is to describe the results of acute cerebral anoxia in adults as a reversal sign.

Methods: We retrospectively examined the CT and MR images of 9 patients in a vegetative state due to acute prolonged anoxia. Each of them had at least one MRI and 4 CT exams 6-12 hours, 10-14 days, 6-8 months and 1 year after the anoxic event. The degree of the cerebral atrophy and the mean density values of cerebral white matter were measured and calculated to demonstrate quantitative changes over time.

Results: We detected a diffuse density decrease of cerebral cortical gray and white matter with a decreased or lost gray/white matter interface and relative preservation of the densities of the thalami, brain stem and cerebellum in CT scans. In addition to CT findings, we found hyperintense areas in periventricular white matter on T2W SE sequences probably due to myelin loss, glial proliferation, microinfarcts and extracellular edema, and bright signals on T1W SE sequences due to paramagnetic pigment deposits.

Conclusions: As a result, we thought that the reversal sign was a characteristic finding of the ischemic state of the adult brain in CT, and it demonstrated irreversible brain damage and carried a poor prognosis.

Key Words: Reversal sign, computed tomography, magnetic resonance imaging, brain damage, cerebral anoxia

Introduction

When cerebral blood flow was interrupted completely, there was a distinctive CT appearance in some of the patients, termed reversal sign. The reversal sign has been described in the literature, for anoxic/ischemic states observed in children due to birth asphyxia, drowning, status epilepticus, meningitis or degenerative encephalitis (1,2). This sign expressed diffuse density decrease of cerebral cortical gray and white matter with a decreased or lost gray/white matter interface or less frequently reversal of the gray/white matter densities (1-3). The densities of the thalami, brain stem and cerebellum were relatively increased (1,2). The reversal sign has not previously been described for adults in the literature.

The aim of this study was to describe the radiological appearance of acute prolonged cerebral anoxia as an adult form of the reversal sign, by using long-term CT and MRI results; to review its mechanism; and to emphasize its effects of it on prognosis.

Materials and Methods

We reviewed 9 patients (7 female, 2 male) with a mean age of 43 years (range 21-67 years). The conditions of 7 of them were due to prolonged intraoperative cardiopulmonary arrest. They had all resuscitated 1-3 minutes after the arrest. Two of them had survived suicide attempts by hanging. We had no certain information about the duration of their anoxic states.

All of them had at least one MRI and 4 CT examinations. CT was performed in all patients 6-12 hours, 10-14 days, 6-8 months and 1 year later. All axial CT scans were obtained with a Siemens Somatom DRH scanner (Erlangen, Germany) with contiguous 5 mm slices in the posterior fossa and 8 mm in the cerebrum. The degree of cerebral atrophy was measured in every patient according to the criteria listed in Table 1, modified by Lange et al. (4). In every CT examination of each patient, the mean density values of the supraventricular

white matter in HU (arithmetic mean of five measurements obtained from periventricular white matter) were calculated to show the quantitative changes in the density of the white matter over time.

In all patients, a single MRI examination made after a period of 9-12 months following the initial CT examination was used for comparison. The axial, sagittal and coronal T1W (15/600 ms) SE sequences, and axial proton density (PD) (12/2000 ms) and T2W (80/2000 ms) SE sequences of each patient were studied with a 1.5 T superconducting magnet (Magnetom, Siemens, Erlangen, Germany).

CT and MR images were analyzed by two radiologists independently. They examined the density differences between the gray/white matter, basal ganglia, brain stem and cerebellum; ventricular shape and size; and the enlargement of the extraaxial cerebrospinal fluid spaces and cisterns. The indexes listed in Table 1 and the mean density values of the periventricular white matter were measured and calculated. The significance of the differences in the indexes and the mean density values over time were analyzed by Friedman two-way Anova test.

Table 1. Indexes for cerebral atrophy.

	Normal	Slight	Moderate	Severe
Huckmann index	≤ 5	5.1-6.4	6.5-7.9	≥ 8
Width of third ventricle (mm)	≤ 7	8-10	11-14	≥ 15
Pars centralis index	≥ 4.1	4.0-3.6	3.5-3.0	≤ 2.9

Results

The initial CT examination results of all patients were normal (Fig. 1). All indexes were normal, and the mean density values of the white matter were within the normal range of 29.7-34.4 HU.

In CT scans taken 10-14 days after prolonged anoxia, there were slight diffuse hypodensities in periventricular white matter with normal gray/white matter interface (Fig. 2). There were no or only slight changes in the indexes of the ventricular system. A slight decrease in the density of the periventricular white matter was detected, ranging from 22.7 HU to 29.0 HU.

There were diffuse hypodensities in periventricular white matter, with relative sparing of gray matter and the gray/white matter interface, and relative hyperdensity in the thalami, brain stem and cerebellum in CT scans taken 6-8 months after prolonged anoxia (Fig. 3). There was slight to moderate cerebral atrophy according to the criteria mentioned above, and also a marked decrease in the density of the periventricular white matter at 16.0-24.5 HU.

In late stages, diffuse cerebral and cerebellar atrophy, moderate to severe ventricular dilatation, marked hypodensity of gray and white matter, decrease or loss of gray/white matter interface, and, in the basal ganglia region, hyperdensity due to calcifications or sparing areas from the ischemia were detected (Fig. 4). The indexes of the ventricular system were impaired seriously and the mean densities of the periventricular white matter were markedly reduced (Table 2).

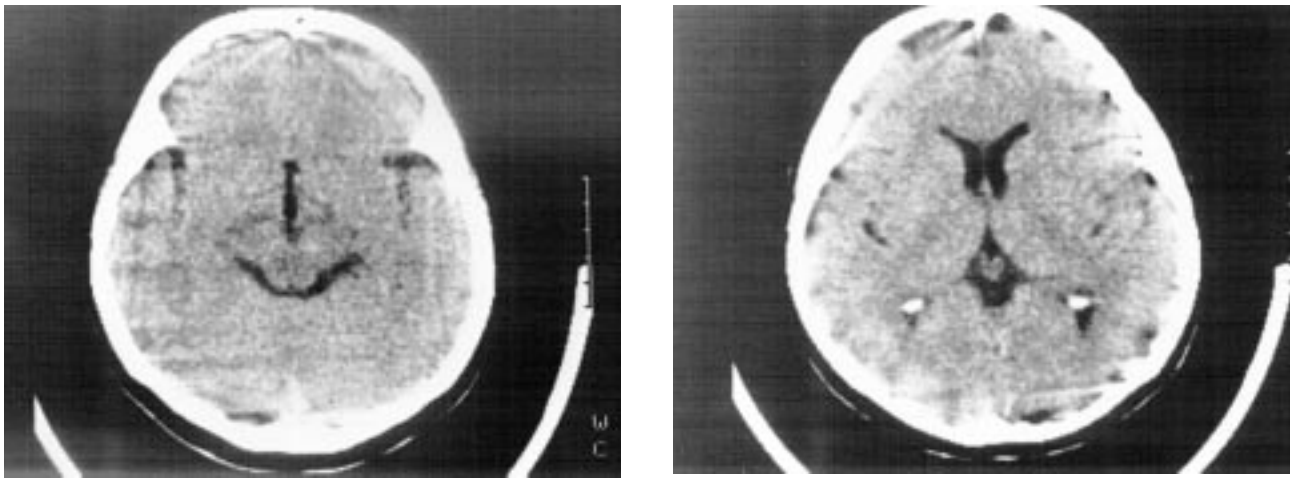

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Figure 1. Initial axial CT scans (A-B) show no pathological changes. Due to the unconsciousness of the patient, some motion artifacts are seen.

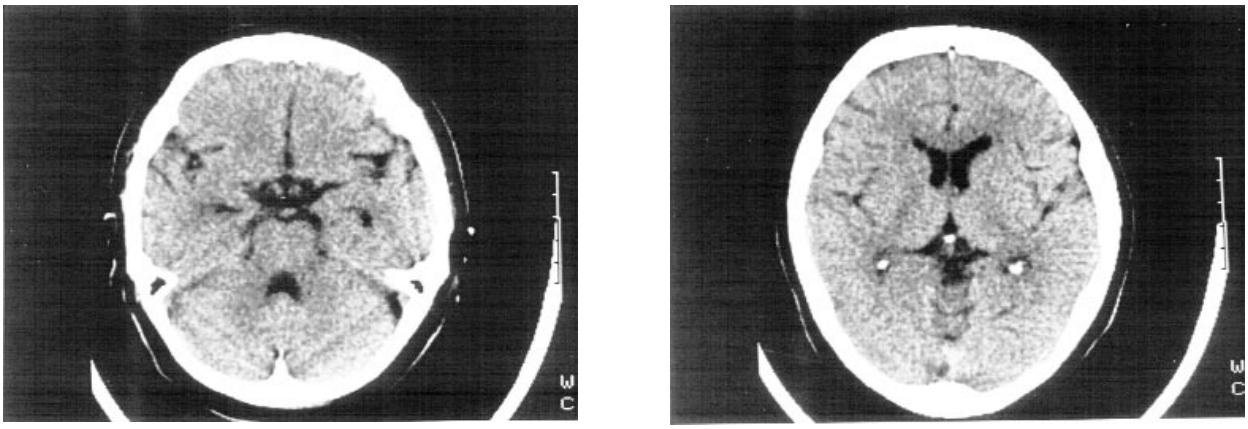

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Figure 2. Axial CT scans (A-B) taken 12 days after the prolonged anoxia show mild diffuse hypodensity in white matter, especially in the periventricular region of the anterior horns.

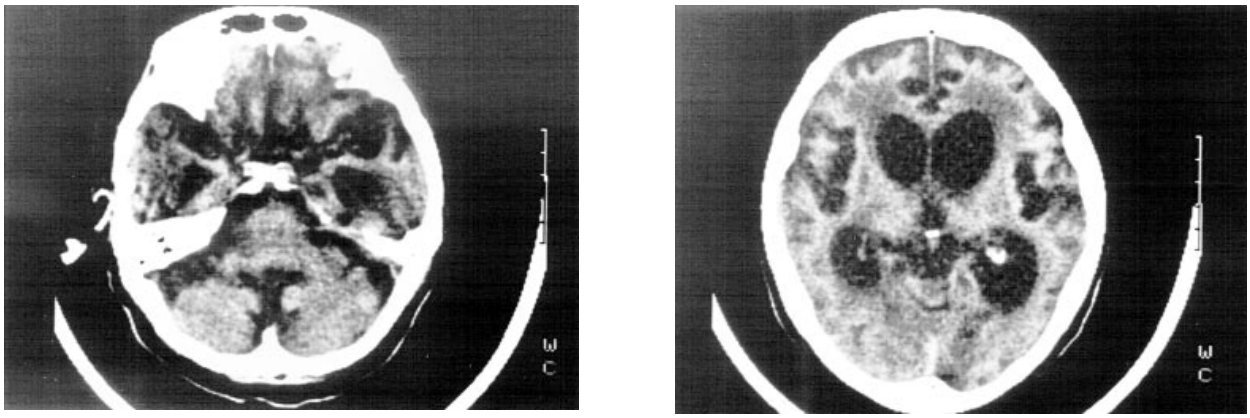

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Figure 3. Axial CT scans (A-B) taken 6-8 months after prolonged anoxia show diffuse hypodensity in white matter with relative sparing of gray matter, relative hyperdensity in the thalami, brain stem and cerebellum, and cerebral and less cerebellar cortical atrophy.

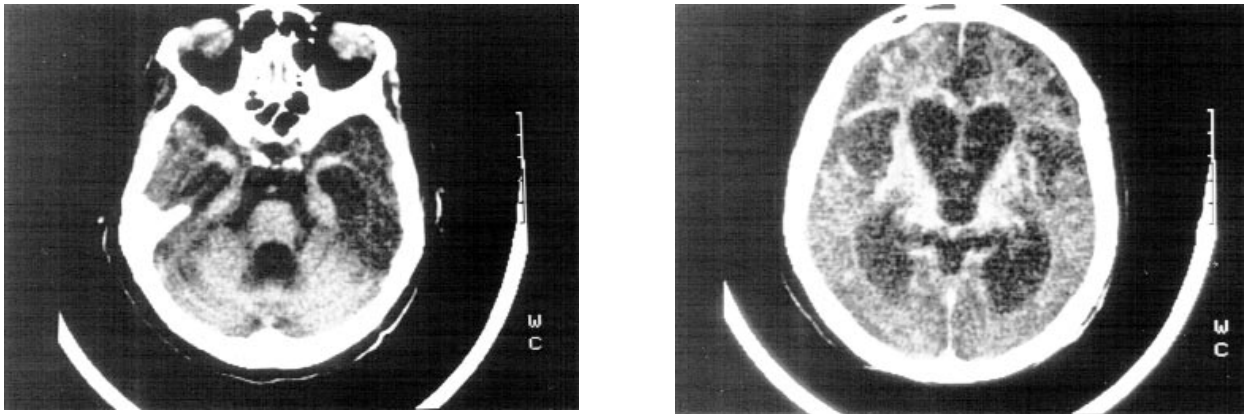

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Figure 4. Late follow-up axial CT scans (A-B) show diffuse bihemispherical cerebral and cerebellar cortical atrophy, ventricular dilatation, marked hypodensity of gray and white matter with relative hyperdensity in the thalami, brain stem and cerebellum, and loss of gray/white matter interface. In the basal ganglia region, there were also small hypodense areas due to microinfarcts with small, patchy, hyperdense areas due to pigment deposition.

Table 2. Distribution of indexes and mean periventricular white matter densities.

No	6-12 hours after anoxia				10-14 days after anoxia				6-8 months after anoxia				1 year after anoxia			
	I	II	III	HU	I	II	III	HU	I	II	III	HU	I	II	III	HU
1	5.0 (N)	3 (N)	4.5 (N)	29.7	5.8 (SL)	5 (N)	4.0 (SL)	22.7	9.2 (SV)	8 (SL)	3.2 (M)	16.0	9.9 (SV)	11 (M)	2.6 (SV)	12.6
2	4.9 (N)	2 (N)	4.1 (N)	33.3	4.9 (N)	2 (N)	4.1 (N)	28.7	7.8 (M)	7 (SL)	3.9 (SL)	24.5	12 (SV)	10 (SL)	3.4 (M)	16.4
3	5.0 (N)	2 (N)	4.1 (N)	31.4	5.5 (SL)	5 (N)	3.8 (SL)	27.9	8.3 (SV)	9 (SL)	3.0 (M)	23.5	10 (SV)	11 (M)	2.8 (SV)	17.6
4	4.8 (N)	4 (N)	4.1 (N)	29.9	5.2 (SL)	6 (N)	3.8 (SL)	26.5	7.1 (M)	7 (SL)	3.5 (M)	23.9	8.4 (SV)	10 (SL)	3.2 (M)	17.4
5	4.9 (N)	3 (N)	4.4 (N)	32.3	5.4 (SL)	6 (N)	3.9 (SL)	27.6	7.5 (M)	8 (SL)	3.6 (SL)	22.6	8.9 (SV)	9 (SL)	3.3 (M)	16.8
6	4.9 (N)	3 (N)	4.4 (N)	34.4	5.1 (SL)	4 (N)	4.3 (SL)	27.3	6.8 (M)	7 (SL)	4.0 (SL)	21.0	8.0 (SV)	8 (SL)	3.5 (M)	17.3
7	5.0 (N)	4 (N)	4.1 (N)	29.8	5.7 (SL)	6 (N)	3.6 (SL)	27.4	9.3 (SV)	9 (SL)	3.0 (M)	18.9	9.5 (SV)	10 (SL)	2.7 (SV)	13.9
8	5.0 (N)	5 (N)	4.2 (N)	31.0	5.5 (SL)	7 (N)	3.8 (SL)	26.9	7.3 (M)	8 (SL)	3.3 (M)	19.8	10.1 (SV)	10 (SL)	29. (SV)	14.9
9	4.9 (N)	3 (N)	4.1 (N)	34.4	5.2 (SL)	6 (N)	4.0 (SL)	29.0	7.6 (M)	7 (SL)	3.7 (SL)	22.8	8.5 (SV)	9 (SL)	3.5 (M)	17.1

I: Huckmann index
II: Width of third ventricle (mm)
III: Pars centralis index
HU: Mean density of periventricular white matter in Hounsfield unit
N: Normal
SL: Slight
M: Moderate
SV: Severe

Initial changes were noticed in the Huckmann index, followed by the pars centralis index and the width of the third ventricle. The decrease in the density of the periventricular white matter was accompanied by the changes in the indexes, but appeared before them. In the Huckmann index and the width of the third ventricle, the values increased over time, the differences were statistically significant ($p<0.0001$), and the major differences were noticed between 10-14 days and 6-8 months after anoxia. In the pars centralis index and the mean density values of periventricular white matter in HU, the values decreased over time, the differences were statistically significant ($p<0.0001$), and the major differences were noticed between 10-14 days and 6-8 months after anoxia.

As in the CT findings, cerebral atrophy and ventricular dilatation were found in the MR images. There were also marked hyperintense areas in periventricular white matter on T2W SE sequences probably due to myelin loss, glial proliferation, microinfarcts or extracellular edema. The pigment deposits were shown as hypointense or signal-void areas on T1 and T2W SE sequences, especially in the basal ganglia. But in two patients, there were bright signals on T1W SE sequences due to paramagnetic pigment deposition in the necrotic ground (Fig. 5).

All patients had 4-7 points according to the Glasgow coma scale, and were staged as group four coma in disabled or vegetative state within 6-8 months after the event. The survival periods of the patients were between 14 months and 9 years with a mean of 5.7 years. Seven patients were still alive and in a vegetative state without any need of life-support systems. Two patients died, 14 and 18 months after the initial CT examinations; as they were outpatients, it was not possible to carry out pathological examinations. At this point, none of the patients had demonstrated any significant recovery, with

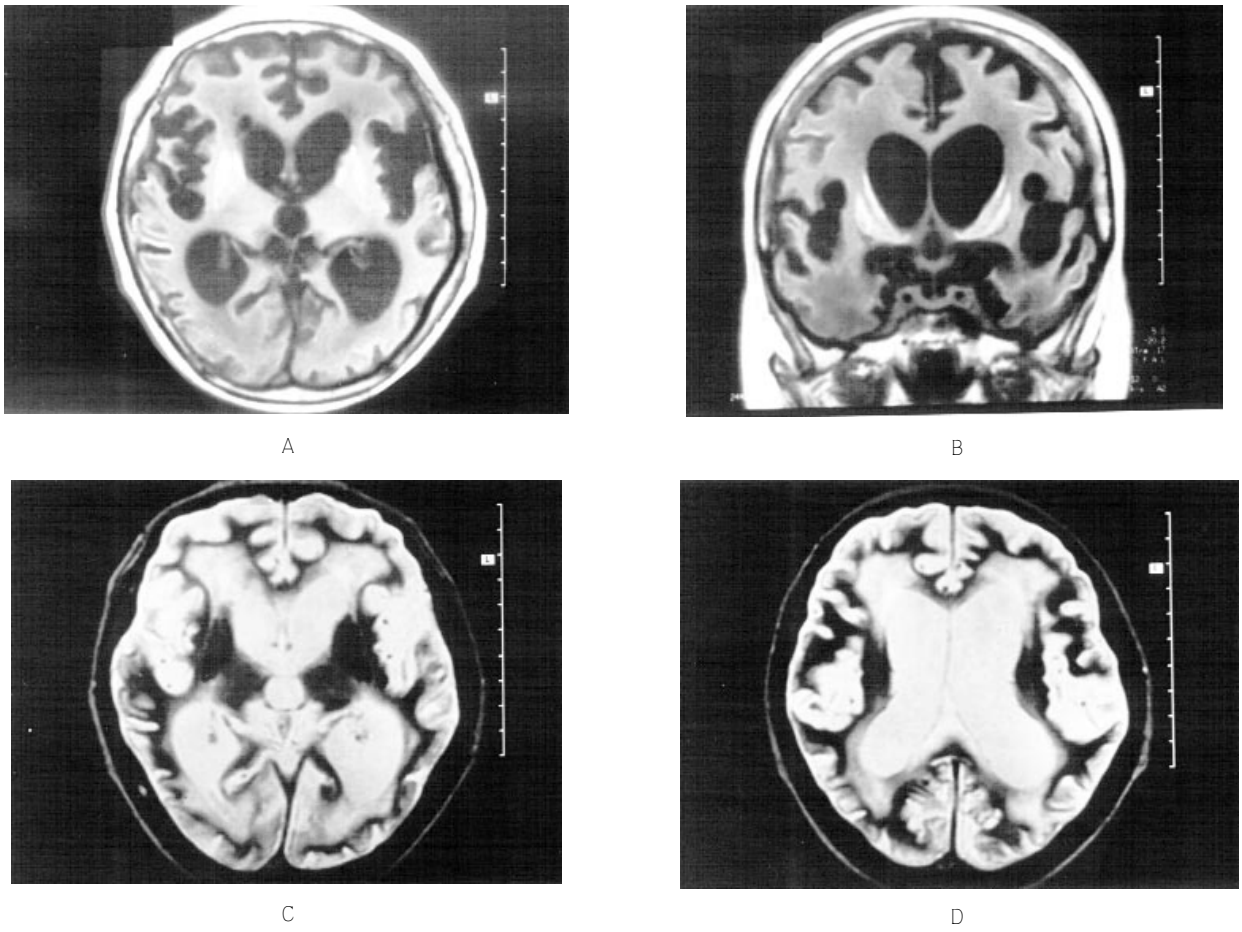

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Figure 5. (A) Axial, (B) coronal, T1W (15/600 ms), and (C-D) axial T2W (80/2000 ms) SE sequences show bihemispherical cerebral and cerebellar atrophy and ventricular dilatation; hyperintensity in periventricular white matter on T2W SE sequences probably due to myelin loss; glial proliferation; microinfarcts; and extracellular edema. There were signal void regions on T2W and hyperintense regions on T1W SE sequences probably due to pigment deposition in necrotic ground especially in the putamen, head of the caudate nucleus and periventricular area. The correlated well with CT appearance (Fig. 4B).

progressive radiological and neurological deterioration in all.

Discussion

Mild diffuse density decrease of periventricular white matter was detected after 10-14 days, due to reperfusion hyperemia and redistribution of extracellular fluid (ECF). In this acute/subacute stage, the decrease in density was more prominent than that in volume. The involved gray matter was usually isodense during the acute phase, because reperfusion hyperemia during this period counterbalanced the basic ischemic low-density tissue changes.

In acute ischemic state, the brain blood flow is greatly interrupted and oxygen consumption is acutely reduced. When the ischemia is sufficiently severe and/or prolonged (more than 5 minutes), parenchymal necrosis begins. The first sign of this damage is redistribution of ECF content, leading to an increase in intracranial pressure (5,6). Impaired circulation with increased tissue resistance due to redistribution of ECF leads to deprived perfusion, fading towards the cortical surfaces (1,6,7). It was also noticed that the elevation of cerebral serum glucose concentrations during the anoxic state caused preferential damage to the convexity of the cerebral cortex and basal ganglia, with relative preservation of the thalami and brain stem (1,3,8).

While the deprivation of cerebral perfusion causes an ischemic state in the peripheral regions (gray and white

matter), it also causes a hypoxic state in the centrally located areas (hypothalami and brain stem). The cellular pathophysiology of these two situations is quite different, and the brain has very different sensitivities to them. Neurons are actually quite tolerant to pure hypoxia and capable of substantial anaerobic respiration, but are especially vulnerable to ischemia (5,6).

If the patient was still alive after the acute phase, marked dilatation of the lateral ventricular system and cortical sulci would develop during the next few months and previously isodense regions would become hypodense. The volume and density of cerebral white matter decreased within 6-8 months. In this situation, the densities of the thalami, cerebral nuclei, brain stem and cerebellum were spared and although the mentioned areas demonstrated their own normal densities, they were seen as relatively more dense than the brain parenchyma in CT scans. In MRI, hypointense areas were also detected in the brain parenchyma as well as in the basal ganglia, thalami, brain stem and cerebellum, due to microinfarcts or to calcifications. This stage included changes probably due to myelin loss and neuronal necrosis.

The reversal sign was believed to result from an accumulation of venous and capillary blood in the white matter; the blood accumulated because venous drainage was impaired by the increased intracranial pressure (3,9). Diffuse decreased attenuation of cerebral hemispheres with relative preservation of density in the thalami, brain stem and cerebellum were explained by Shevmon as postischemic increased capillary proliferation in the regions of normally high metabolism due to ischemia (7). Myers also showed relative preservation of central areas of the brain in experimentally asphyxiating newborn monkeys and extensive tissue necrosis of all areas of the cerebrum expect for the thalami, hypothalami and medial temporal lobes after 6 days (10). He explained this preservation by transtentorial herniation during the acute stage. Transtentorial herniation caused a decrease in tissue pressure and an increase in tissue perfusion of the herniated regions and prevented tissue necrosis of the centrally placed regions that contained respiratory and circulatory autonomic centers. This theory also explained how these patients had such long survival times in a vegetative state.

Preservation of the cerebellum might be due to pressure differences between the middle and posterior cranial fossa. The posterior fossa has a lower pressure and is less affected by the increase in intracranial pressure. This acute redistribution of cerebral perfusion may be affected by autonomic regulation with preference to centrally located areas (thalami, brain stem). These aforementioned regions contain main auto-regulatory areas such as vasomotor and respiratory centers which are mainly located in the reticular system of brain stem, and get their blood flow through terminal perforator arteries that are small but numerous. Also they do not have large venous drainage systems as cerebral hemispheres do, so the perfusion time of the blood is longer than that of the cerebral hemispheres. These anatomical differences probably preserve these central regions during the anoxic state.

In the chronic stage, diffuse cerebral and cerebellar atrophy, ventricular dilatation, marked hypodensity of gray and white matter, and loss of the interface of the gray/white matter densities were detected. In the basal ganglia region, there were small hypodense areas due to microinfarcts with small, patchy, hyperdense calcifications. This phase represented the irreversible stage of the ischemic encephalopathy, i.e., the hemispheres were dead, but the brain stem was still alive. These changes seen in the brain depended on the duration and intensity of the ischemia and on the period of survival.

The periventricular white matter is usually the most severely affected area in patients with irreversible brain injury (5). MRI, PD and T2W SE sequences show hyperintensity in these regions before CT findings (5,11,12,13). High signal intensity is seen on T2W SE sequences at the sites of increased water content within brain parenchyma. Ischemia without infarction causes periventricular hyperintensity (5,11,12,13). Ischemic lesions involving the deep white matter are histopathologically characterized by loss of myelin, axons, and oligodendroglial cells (12). While there may be mild reactive gliosis and hyaline fibrosis of arterioles, necrosis and cavitation are absent, thus differentiating these ischemic areas from true infarctions (12). The loss of myelin and tissue produces a hypodensity change on CT along with enlargement of sulci and ventricles. High signal intensity is found on the T2W SE sequences while low signal intensity is found on the T1W SE sequences.

Calcifications are generally shown as hypointense or signal void on SE sequences, especially on T2W SE

sequences. Bright signals on T1W and signal-void areas on T2W SE sequences, especially in the basal ganglia, were due to mineralization with paramagnetic elements (e.g., manganese, copper, iron) or to deposition of calcium hydroxiapatite on necrotic or degenerated ground, and to subacute hemorrhage (13-15). The timing of our examination cancelled out the probability of subacute hemorrhage. It was highly probable that the bright signal on T1W SE sequences was due to mineralization with paramagnetic ions onto necrotic ground, as the mineralized areas correlated with CT findings.

We did not detect the massive brain edema and rapid changes defined in Han's classification. The earliest time of detection of slight hypodensity in periventricular white matter was about 10-14 days after the initial examination, probably due to redistribution of ECF content. The classification and progression of the reversal sign in adults were quite different from those of the neonates and therefore Han's classification was not meaningful for adults. The major reason for these differences was probably the different response mechanisms of the mature brain from those of the immature neonatal brain to anoxia. The pattern of brain injury from hypoxic-ischemic injury in children after the neonatal period differed from that seen in neonates (3). The reasons for this change were not entirely clear, but were almost certainly related to the physiological and biochemical changes that occurred during brain maturation; these led to different patterns in metabolic activity at different ages in the maturing brain (16). Relative preservation of central regions is probably due to different anoxic stages of the brain and brain stem. The reversal sign is a characteristic finding of the ischemic state of the adult brain in CT, and it demonstrates irreversible brain damage and carries a poor prognosis.

References

1. Han BK, Towbin RB, DeCourten-Myers G, McLaurin RL, Ball WS. Reversal sign on CT: effect of anoxic/ischemic cerebral injury in children. AJNR 10:1191-8, 1989.
2. Cohen RA, Kaufman RA, Myers PA, Towbin RB. Cranial computed tomography in the abused child with head injury. AJNR 6:883-8, 1985.
3. Barkovich AJ. Pediatric neuroimaging. Lippincott-Raven. Philadelphia 1996, pp:107-175.
4. Lange S, Grumme T, Kluge W, Ringel K, Meese W. Cerebral and spinal computerised tomography. Basel, Schering; 1989, pp:104.
5. Goldberg HI, Lee SH. Stroke. Cranial MRI and CT (Eds. Lee SH, Rao KCVG, Zimmerman RA) McGraw Hill Inc. New York 1992, pp:623-700.
6. Morris JH, Schoene WC. The Nervous system. Pathologic basis of disease (Eds. Robbins SL, Cotran RS, Kumar V) WB Saunders. Philadelphia, 1984, pp:1370-1436.
7. Shewmon DA, Fine M, Masdeu JC, Palacios E. Postischemic hypervascularity of infancy: a stage in the evolution of ischemic brain damage with characteristic CT scan. Ann Neurol 9:258-265, 1981.
8. Myers RE, de Courten-Myers GM. Metabolic principles of patterns of perinatal brain injury. Risks of labour (Ed. Crawford JW). Wiley. New York 1985, pp:119-146.
9. Bird CR, Drayer BP, Gilles FH. Pathophysiology or reverse edema in global cerebral ischemia. AJNR 10:95-98, 1989.
10. Myers RE. Experimental models of perinatal brain damage: relevance to human pathology. Intrauterine asphyxia and developing brain (Ed: Gluck L) Yearbook Medical. Chicago 1977, pp:37-97.
11. Edwards-Brown MK, Bonnin JM. White matter disease. Magnetic resonance imaging of brain and spine (Ed. Atlas SW) Lippincot-Raven. Philadelphia 1996, pp:649-706.
12. Brun A, Englund E. A white matter disorder in dementia of the Alzheimer type: A pathoanatomical study. Ann Neurol 19:253,1986.
13. Barkovich AJ, Atlas SW. Magnetic resonance of intracranial haemorrhage. Radiol Clin North Am 26:801-820,1988.
14. Atlas SW, Grossman RI, Hackney DB, et al. Calcified intracranial lesions: Detection with gradient-echo-acquisition rapid MR imaging. AJR 150:1383-9,1988.
15. Inoue E, Hori S, Narumi Y, et al. Portal systemic encephalopathy; Presence of basal ganglia lesions with high signal intensity on MR images. Radiology 179:551-5, 1991.
16. Chuangi HT, Phelps ME, Mazziotta JC. Positron emission tomography study of human brain functional development. Ann Neurol 22:487-97, 1992.