INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Prognostic Value of Magnetic Resonance Imaging in Post-Resuscitation Encephalopathy

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Abstract

Objective Prediction of the prognosis of comatose survivors after cardiopulmonary arrest (CPA), so-called post-resuscitation encephalopathy (PRE), relies on neurological examination findings. Early laboratory indicators of poor prognosis (vegetative state/death) are not sensitive enough.

Methods We analyzed the results of magnetic resonance (MR) imaging with fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) in 22 consecutive patients with PRE. Clinical details such as arrest place and anoxia time along with neurological examination findings including items of Glasgow coma scale (GCS) and the Full Outline of UnResponsiveness (FOUR) score were determined. Receiver Operator Characteristics (ROC) curves were produced to determine prognostic yield of the parameters studied.

Results Prognosis was classified as 'poor' (Glasgow-Pittsburg Cerebral Performance —CPC-score 4 or 5) in 16 and 'better' (CPC score 1-3) in 6 patients. The lower limit of confidence interval (CI) of the area under the curve (AUC) of the ROC was higher than 0.5 for visual, motor and total scores of GCS and FOUR score. Presence of a lesion pattern of multilobar, or diffuse, cortical involvement, termed as "extensive cortical lesion pattern" in MR imaging was a very good predictor of poor prognosis with an AUC of ROC of 0,937. Sensitivity of GCS motor part score and MR was 87.5% (95% CI: 61.6%-92.6%). Motor part of the FOUR score has a slightly lower sensitivity (68.7% with 95% CI from 41.4% to 88.9%). Incorporating of MR to the motor scores (either GCS or FOUR score) improved sensitivity to 100 % (95% CI: 79.2%-100%). AUC of the ROC was 1.000 (95%CI: 0.844-1.000) for the combination of MR and GCS motor score.

Conclusion This study provides the preliminary evidence that MRI, when used in conjunction with a neurological examination, may have potential in terms of predicting outcome in patients with PRE.

Key words: magnetic resonance imaging, prognosis, diffusion-weighted imaging, FLAIR, FOUR score, cardiopulmonary arrest, vegetative state

(Inter Med 48: 1635-1645, 2009)
(DOI: 10.2169/internalmedicine.48.2091)

Introduction

Anoxic-ischemic encephalopathy following cardiopulmonary resuscitation (CPR), so-called Post-Resuscitation Encephalopathy (PRE), is a relatively frequent dramatic condition. PRE is introduced as a term to describe the comatose state after CPR (1). It is believed that the possibility of awakening with good neurological prognosis significantly decreases in the patients who are still in the comatose state after 3 days following CPR (2). These patients often remain in long-standing vegetative or minimally conscious state. The economical and moral effects originating from the long-term care of these severely disabled patients are of vital importance.

Determination of the patients with PRE who have no chance of good prognosis is a critical point. Accurate knowledge of the prognosis is definitely useful for determining the level of care. For prediction of outcome in PRE patients, several clinical and laboratory findings have been re-

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Received for publication January 24, 2009; Accepted for publication May 27, 2009
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ported to be useful (3). First, the circumstances surrounding CPR such as anoxia time (duration from collapse to initiation of CPR, the critical cut-off is 5 minutes), arrest place (out of hospital or in hospital), duration of CPR (time between the initiation of CPR and reestablishment of spontaneous systemic circulation, the critical cut-off is 20 minutes), type of arrest (cardiac, pulmonary, or both), type of cardiac arrest arrhythmia (ventricular fibrillation, asystole, electromechanical dissociation) are all related to the poor outcome, but none of them can predict poor outcome satisfactorily alone or in combination (3). Secondly, neurological examination findings including items of Glasgow Coma Scale (GCS), pupillary light reflexes, corneal reflexes, reflex (oculocephalic and oculovestibular) or spontaneous eye movements, sustained eye deviation especially upward, and the presence of seizures or myoclonus are important. Briefly, absent pupillary and corneal reflexes from day 1 to 3 after CPR, myoclonus status epilepticus (MSE) within the first day, and absent or extensor motor responses after 3 days show a satisfactory level of certainty (almost zero false-positive rate) for selection of patients with a poor prognosis (3). We think that these criteria are inevitably useful but may exert some of the following problems: 1) Confusion, especially in the evaluation of the pupillary light response, can arise from drugs with effects on the autonomic nervous system, used during or after CPR. 2) Sedatives and neuromuscular blockers used for intubation or during therapeutic hypothermia can obscure the examination reliability. 3) Most of these findings, such as MSE and upward deviation of the eyes, are disturbingly rare (about 20%) (4), and 4) perhaps the most important, problem is that these findings cannot determine the patients surviving in persistent vegetative or minimally conscious state, albeit they are very reliable in the prediction of mortality.

Thirdly, neurophysiological studies such as electroencephalography (EEG) and somatosensory evoked potentials (SEP) are valuable in determining prognosis. The association of the presence of four malignant EEG patterns (generalized suppression, burst-suppression, periodic generalized complexes and alpha coma) and individual poor prognosis is strong, but remains insufficient to predict a poor prognosis with zero mistake (False positive rate for poor outcome was reported as 3%) (3). On the contrary, bilateral absence of N20 component of median SEP has more acceptable false positive rate (0.7%) in accurate prediction when recorded between the first and the third day following CPR (3). However electrophysiological tests are prone to technical artifacts (especially for SEP when performed in the intensive care unit), and can be significantly affected by drugs and systemic metabolic perturbations (especially for EEG).

Fourth, biochemical markers including neuron-specific enolase (NSE) and astroglial S100 protein in serum and cerebrospinal fluid (CSF) as well as creatine kinase brain isoenzyme and neurofilament in CSF are useful. Among these, only increased (>33 microgram/L) serum NSE levels at the first and third post-CPR days seems to be a useful biomarker for poor outcome prediction (3).

Finally, neuroimaging may be important in prognostification of PRE patients. A cranial computerized tomography (CT) is usually performed to exclude primary CNS injury resulting in arrest. During the early period after CPR, it usually reveals no abnormality in the patients without primary CNS events. But, ischemic changes and progressive brain edema become evident later (usually on the second day). Magnetic resonance (MR) imaging is superior to CT in terms of documentation of early ischemic and edematous changes. Perhaps due to safety concern about transport to, and staying in, the MR suits, the reported experience with MR imaging in PRE patients remains limited (4-12). There is a consensus that conventional MR imaging findings are not a good prognostic indicator (13). However, some studies have reported that fluid attenuated inversion recovery (FLAIR) imaging and newer MR techniques, particularly diffusion-weighted imaging (DWI), are valuable tools (4, 5, 12). These studies suggested that comatose CPR survivors with diffuse cortical signal changes on these examinations have an invariably poor prognosis (Fig. 1). On the other hand, some studies did not support this argument (8, 14). Accordingly, a recent practice parameter concluded that there was insufficient evidence to precisely delineate lesions on MR study or CT that would conclusively predict poor outcome, and suggested further studies (15). On the ground of this information, we herein report our experience with DWI and FLAIR imaging as a tool for prognostication in patients remaining comatose after CPR.

Patients and Methods

Twenty-two comatose CPR survivors who underwent brain MRI at the discretion of their treating physicians were included in this review. This case series, which was prospectively gathered and retrospectively analyzed, includes all patients with PRE, whom a brain MR study was obtained during their hospital stay, between December 2006 and May 2008. All were on mechanical ventilation during imaging. MR study included DWI (TR/TE; 2,800/78 ms, max b value of 1,000 s/mm^2 and FLAIR (TE/TR/TI; 8,500/98/2,150 ms) sequences in all patients. Four patients also had follow-up MR examination. These studies were performed according to routine clinical practice on one of the two 1,5 Tesla scanners available at our institute (Symphony, Siemens, Erlangen, Germany and Achieva, Philips, Netherlands). No adverse clinical event attributable to imaging was experienced during or following MR examination. Of note, a physician accompanied and monitored the patient during the scanning as per routine protocol used in our hospital. The MR images were evaluated by an experienced neuroradiologist (KKO) without the knowledge of any of the outcome features on a retrospective basis.

Characteristics of arrest assessed were arrest place (in- and out-hospital), anoxia time (as shorter or longer than 5 minutes), type of arrest (as cardiac arrest or primary pulmo-

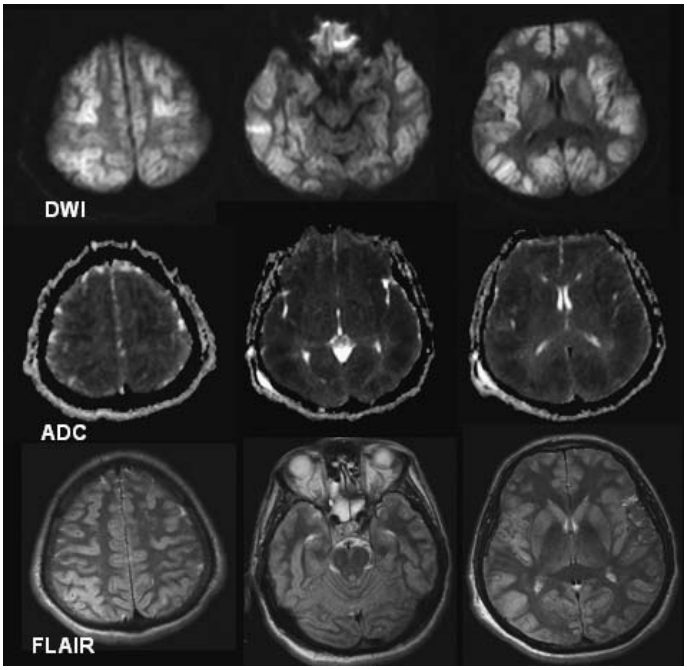

Figure 1. **Representative example of extensive cortical (plus subcortical) injury pattern. Lesions are bright in DWI (diffusion-weighted imaging) (upper row), dark in ADC (apparent coefficient mapping) (middle row) and hyperintense in FLAIR (fluid attenuated inversion recovery) sequences (bottom row).**

nary followed by cardiac arrest) and duration of CPR (as shorter or longer than 20-minutes). Resuscitation variables were selected in accordance with recommended guidelines (16). Initial cardiac rhythm, interventions performed and immediate predisposing factors were also collected, but not further analyzed due to significant homogeneity across the study population. For example, all patients have asystole as initial cardiac rhythm except one with ventricular fibrillation and another with pulseless electrical activity. And, therapeutic hypothermia was administered for only one particular patient.

Detailed neurological examination including Glasgow coma scale (GCS) (17) and the Full Outline of UnResponsiveness (FOUR) score (18) were performed. The examination findings obtained at the end of the third day were evaluated further except for one particular patient who died on the second day. We also noted the presence of sustained upward eye deviation and any kind of epileptic seizure.

At least one EEG was performed in 17 patients. Complete or near-complete suppression (isoelectric EEG), burst-suppression, generalized periodic epileptiform complexes and alpha coma were considered as four malignant EEG patterns indicating worse prognosis (3).

Prognostic classification was performed according to Glasgow-Pittsburg Cerebral Performance Categories (CPC-scores) (19, 20). We further dichotomized CPC scores 4 and 5 as "poor prognosis" and CPC scores 1, 2 and 3 as" better (than vegetative) survival" (21). Time and main cause(s) of death were also noted for the patients who died. The prognostic evaluation was performed by a neurologist (GB) who was blind to the MR imaging results.

The Institutional Review Board of Hacettepe University Hospitals approved the study protocol, and waived the need for informed consent because of the retrospective nature of the data analyses.

Statistical analysis

All values were given as "mean ± standard deviation", "percentages", and "median" as appropriate. Mann-Whitney *U* and Fisher's exact tests were used to compare groups in terms of numerical and categorical variables, respectively. A *p*-value of lower than 0.05 was set as the statistically significant level.

Receiver Operator Characteristics (ROC) curves were produced to determine the prognostic yield of the clinicoradiological parameters evaluated. ROC curves represent a graph that plots the true positive rate (sensitivity) versus the false positive rate (100-specificity) at various cut-off points. Area under curve (AUC) and its 95% confidence intervals (95% CI) as well as standard error for AUC of the ROC curves were calculated. Sensitivity (and its 95% CIs), specificity (and its 95% CIs) and positive and negative likelihood ratios (+LR and -LR, respectively) for the various cut-offs were defined. We performed binary logistic regression analysis using the presence of MSE and upward gaze deviation as well as MRI involvement pattern (extensive or not) and either the scores of eye, motor and verbal items and total scores of GCS or the scores of visual, brainstem, motor and respiratory items and total scores of the FOUR scale as independents and prognosis as the dependent parameter. The cut-off points of items and total scores of GCS and the FOUR scales were determined as per ROC analyses, and

Table 1a. Clinical Features in Patients with PRE

ID	Age [year] / sex	Place of CPA	CPR initiation time [min]	Type of CPA	Duration of CPR [min]	Glasgow Coma scale				FOUR score					Eye deviation	Epileptic seizure
						E	V	M	T	E	B	R	M	T		
KB	49,F	Out	>5	CP	3	1	1	1	3	0	4	1	0	5	Up	MSE
YT	72,M	Out	>5	CP	20	1	1	1	3	0	4	1	0	5	Mid	MJs
OT	30,M	Out,in	>5, <5	CP,C	>20, 10	1	1	1	3	0	4	0	0	4	Mid	None
AK	32,F	In	<5	PC	30	2	1	4	7	1	4	0	2	7	Mid	None
NE	66,F	Out	<5	CP	20	1	1	1	3	0	4	0	0	4	Mid	None
AI	55,F	In	<5	CP	25	1	1	3	5	0	4	0	2	6	Mid	None
MS	76,M	Out	>5	CP	10	1	1	1	3	0	4	0	0	4	Mid	None
TC	74,F	In	<5	PC	35	1	1	2	4	0	4	0	1	5	Mid	None
UE	72,M	Out	>5	CP	10	1	1	2	4	0	2	0	1	3	Mid	None
HK	29,M	In	<5	CP	105	1	1	3	5	0	2	0	2	4	Up	None
NK	81,F	In	<5	CP	>20	1	1	1	3	0	4	0	0	4	Mid	None
DM	49,M	Out	>5	CP	7	1	1	1	3	0	4	0	0	4	Mid	None
IA	54,M	In	>5	PC	10	2	1	4	7	1	4	1	2	8	Up	MSE
NA	43,M	In	<5	CP	5	2	1	3	6	1	4	1	2	8	Mid	GTCS,MJs
EV	27,F	In	<5	PC	5	1	1	2	4	0	4	1	1	6	Up	MSE
AC	48,M	Out	>5	CP	60	2	1	2	5	1	4	1	1	7	Mid	None
MC	51,M	In	<5	CP	10	2	1	4	7	1	4	1	2	8	Mid	None
NEs	78,F	In	<5	PC	10	1	1	4	6	0	4	0	2	6	To left	None
AO	55,M	In	<5	CP	25	2	1	4	7	1	2	0	2	5	Mid	None
SB	56,M	In	>5	PC	40	3	1	4	8	2	4	2	2	10	Mid	None
OK	60,M	In	<5	PC	<5	3	1	5	9	2	4	1	3	10	Mid	Focal
DC	76,F	In	<5	PC	3	3	1	5	9	2	4	1	3	10	Mid	None

Notes—ID refers to initials of the name of each patient; F, female; M, male; CPA, cardiopulmonary arrest; CPR, cardiopulmonary resuscitation; CP, cardiac followed by pulmonary arrest, C, cardiac arrest; PC; pulmonary followed by cardiac arrest; E, eye or visual; V, verbal; M, motor, T, total or sum, B, brainstem; R, respiratory; MSE, myoclonic status epilepticus, GTCS, generalized tonic clonic seizures, MJs, myoclonic jerks; Focal, focal seizures.

categorized as present and absent. SPSS® 13.0 and MedCalc® statistical package-programs were used for the analyses.

Results

Demographic information, comorbid conditions, resuscitation and imaging variables for each patient are summarized Table 1a and 1b. Representative parts of MR imaging in each patient including repeated studies are given in Fig. 2, 3 and 4.

Of 22 patients with PRE who underwent brain MR imaging, prognosis was classified as "poor" in 16 (mean age: 54±18, female/male ratio: 6/10), and "better" in 6 (mean age: 63±12, female/male ratio: 2/4). In the 16 patients with poor prognosis, 11 died from PRE and/or from the other components of the post-resuscitation syndrome (please see Table 1b). No recovery of mental status and other elements of the neurological functions were observed during their ICU stay. Five patients survived in persistent vegetative state (all five were followed at least 3 months). Four of six patients categorized having better prognosis related to PRE died later. Case-NEs and Case-SB weakened on days 5 and 3, but died on day 16 and 9 from terminal cardiac failure. Case-AO died from multiorgan failure on day 42. His best GCS was 14 before subsequent worsening. Case-DC had a second cardiac arrest, which had not responded to CPR 17 days after the first one. She had reached CPC-1 level prior to this last event. Of the 2 patients discharged, one (case-MC) was in CPC-2 category (significantly amnestic with no motor deficit at discharge, subsequently improved and started to work 8 months after CPR) and the other (case-OK) was in CPC-3 category (spastic quadriparesis with significant amnesia, almost fully dependent state). Of note, during their disease all patients received our best medical management irrespective of the prognostic determination because DNR order and withdrawal of support and care are legally banned in our country.

CPA occurred out of hospital in 7 (44%) of the patients with poor prognosis, and in hospital in the remaining patients and in all patients with better prognosis. There was no bystander CPR in our series. Pulmonary arrest developed first in 4 patients in each group. CPR initiation interval was longer than 5 minutes in 8 (50%) and 1 (17%) patients with

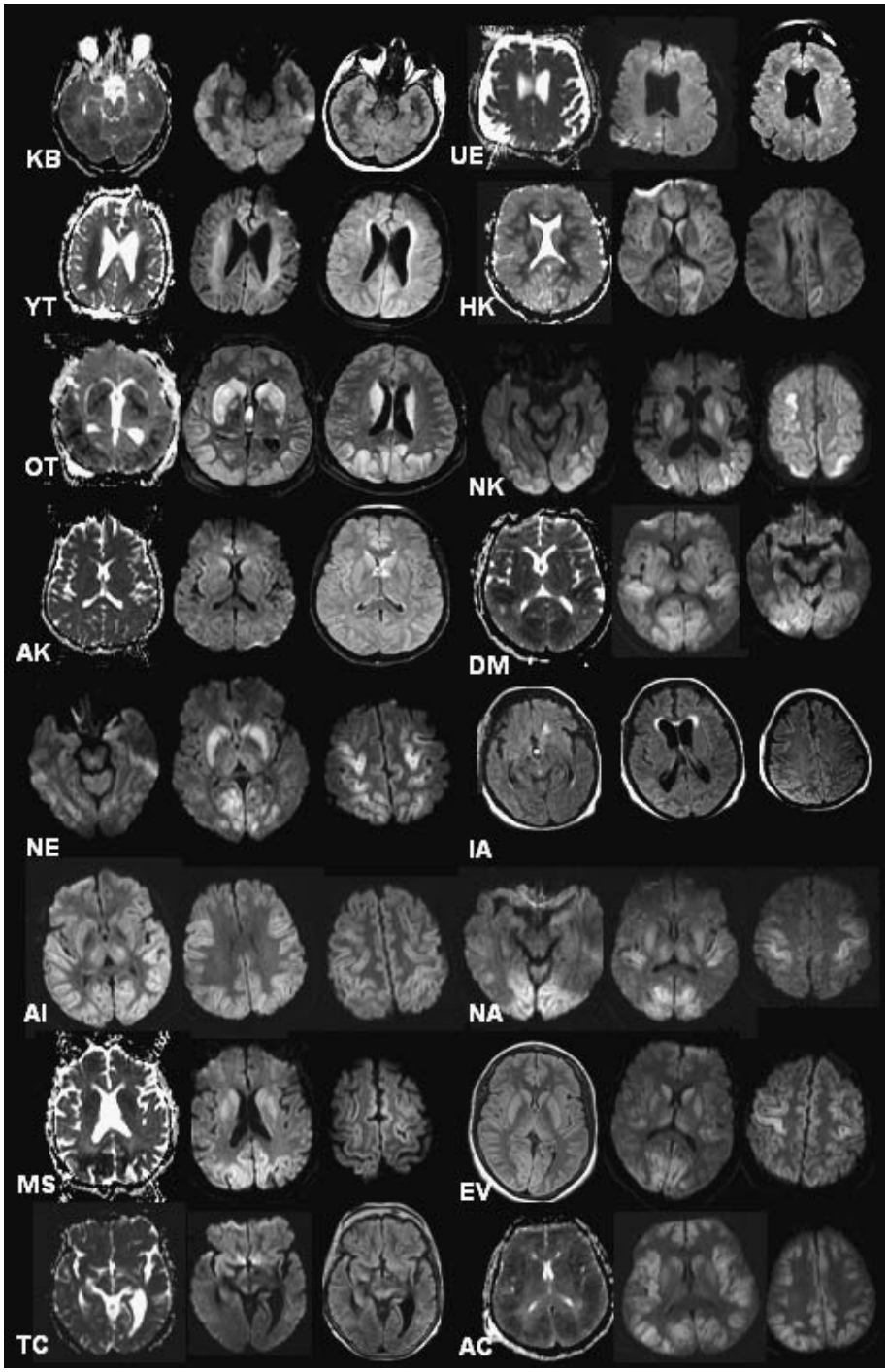

Figure 2. **MRI injury patterns in PRE patients who showed a poor prognosis.**

poor and better prognosis, respectively. CPR duration was longer than 20 minutes in 7 (44%) patients with poor prognosis and in 4 (67%) ones with better prognosis. None of these parameters were significantly different between two groups (Table 2).

Median scores of visual and motor items of GCS and its sum were higher in patients with PRE who survived with a better prognosis. In terms of the FOUR score, brainstem and respiratory items were not different, while visual and motor items as well as the sum of this score were higher in patients with a better prognosis (Table 2). Upward sustained eye deviation and MSE were noted in 25% and 19% of PRE patients with a poor prognosis, respectively, but in none of the others.

Brain CT was performed in one patient of those classified as having better prognosis on the first day and remained normal. In 7 patients with a poor prognosis, brain CT, obtained for 3 patients on day 1, for 3 on day 2 and for 1 on day 3, showed widespread cerebral edema in 2 patients and no abnormality in the remaining patients.

In the patients with a poor prognosis, the median interval from CPR to MR examination was 3,5 days, which is earlier than that in the patients with better prognosis. This trend was not different when considering the time of the follow-

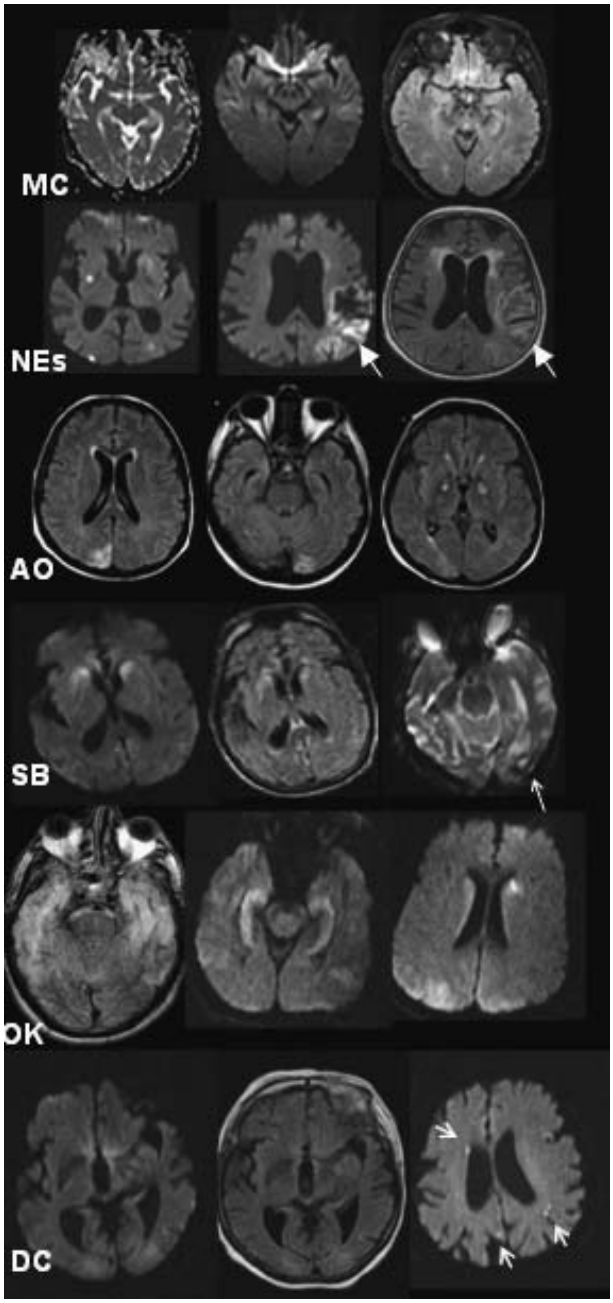

Figure 3. **MRI lesions in PRE patients with a good prognosis. Closed arrow shows left middle cerebral artery inferior division infarct, open arrow shows left occipital hemorrhage, small arrows show small embolic lesions. Eye of the tiger appearance is seen at the third row last picture (AO).**

up imaging rather than the first one (Table 2). An MRI lesion pattern of multilobar, or diffuse, cortical involvement, termed as "extensive cortical lesion pattern" (Fig. 1), were only seen in PRE patients with a poor prognosis. No patients with a better prognosis had this type of involvement evident in their images. Two patients had regional MR abnormalities in the poor prognostic group: lesions like Wernicke's encephalopathy in one (case-TC) and gyral edema along with scattered sulcal hyperintensity in another (case-UE). In patients with PRE resulting in better prognosis, brain MR study revealed predominantly bilateral hippocampal involvement in two (case-MC and case-OK) (Fig. 3). In one of them (case-OK), the medial temporal lobe was also involved extensively but there were no other lobar lesions consistent with aforementioned extensive involvement. One patient (case-AO) showed symmetrical pallidal necrosis (eye of the tiger appearance) along with bilateral occipital ischemic lesions. On MR study of another particular patient with endocarditis (case-SB), bilateral striatal and occipital lesions in addition to left occipital lobar hemorrhage were observed. There were multiple embolic type ischemic lesions in the two remaining patients in the better PRE prognosis group. While brain MRI was otherwise normal in one of them (case-NEs), there were bilateral occipital lesions consistent with PRE in the other (case-DC). Importantly, the lesion pattern in the follow-up MR study showed no cate-

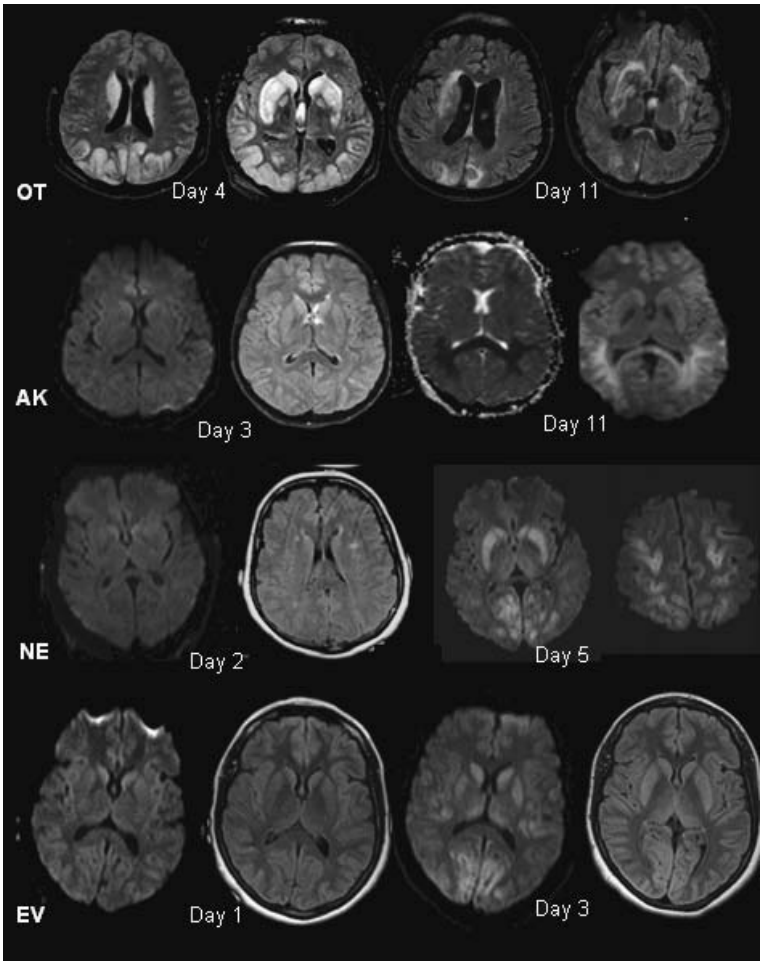

Figure 4. **MRI lesion evolution in PRE patients with follow-up MRI.**

gorical difference except for an increase in the clarity of the lesions (Fig. 4). FLAIR imaging delineated lesions more clearly than DWI in patients who underwent MR examination during the subacute phase. In the acute period, FLAIR generally showed mild accentuation of gray-white matter differentiation in the cortical region and a variable degree of cortical swelling.

Results of ROC analyses are summarized in Table 3. The lower limit of the confidence interval of AUC of ROC was higher than 0.5, which indicates the clinical usefulness of the test, for visual, motor and total scores of the GCS and the FOUR score. The presence of an extensive cortical lesion pattern on MR imaging was also a very good predictor of poor prognosis with an AUC of ROC of 0.937. Similar to the specific MR examination finding studied, motor items of GCS and FOUR score had 100% specificity at the cut-off points [worse than withdrawal response (grade 4) for GCS and worse than any flexion (grade 2) for the FOUR score], however, the lower limit of confidence interval was only 54.1%. The sensitivity of GCS motor part score and MR imaging was 87.5% (95% CI: 61.6%-92.6%). The motor part of the FOUR score has a slightly lower sensitivity (68.7% with 95% CI from 41.4% to 88.9%). Incorporating the MR imaging with the motor scores (either GCS or FOUR score) improved the sensitivity to 100% (95% CI: 79.2%-100%). AUC of the ROC was 1.000 (95% CI: 0.844-1.000) for the combination of MR imaging and GCS motor score. Negative likelihood ratios were good enough for all clinical and radiological parameters (between 0.13 and 0.81). The smallest -LR (0.13) was noted for GCS motor score and MR study. In contrast, none of the criteria reached a sufficient (higher than 5) +LR to be useful clinically. Logistic regression analysis demonstrated that 95.5% of the cases can correctly be classified by the combination of the presence of an extensive lesion pattern on MRI and GCS motor item (3 or less) or the FOUR score motor items (1 or less).

Discussion

Our preliminary study including a consecutive series of comatose CPA survivors confirmed the previous studies implying the potential usefulness of brain MRI with DWI and FLAIR sequences in prognostication of these patients. The appearance of extensive cortical abnormalities in these MRI modalities results invariably in either permanent vegetative state or clinical death (4-6, 12, 22) In other words, there was no patient with PRE who made a reasonable long-term clinical recovery in the presence of this particular MRI lesion pattern. If confirmed in a larger number of patients, a

Table 1b. Associated Diseases, Outcome and Laboratory Features in Patients with PRE

ID	Diseases	EEG	Days to first EEG	Days to MRI	MRI Pattern	Outcome CPC score	Time to exitus/ follow-up [day]	Presumed etiology of Exitus
KB	DM, CAD	BSP	2	2	Extensive	5	4	MOF, sepsis, shock
YT	Larynx cancer	Not done	-	5	Extensive	5	24	MOF, pneumonia
OT	PTE	VS	15	4,11	Extensive	4	>90	-
AK	Myasthenic crisis	VS	13	3,11	Extensive	5	79	MOF, sepsis
NE	AMI	PED	2	2,5	Extensive	4	>90	-
AI	CAD, ARF	Alpha coma	3	4	Extensive	5	7	MOF, shock
MS	DM, CAD, s/p CABG	Not done	-	2	Extensive	5	4	MOF, shock
TC	DM, CAD, Aspiration	VS	11	11	Regional (Wernicke encephalopathy like)	5	21	MOF
UE	AMI	Not done	-	1	Regional (Gyral edema, sulcal hyperintensity)	5	2	Shock
HK	Brachiocephalic vein rupture, PTE	VS	2	11	Extensive	5	25	MOF, shock
NK	DM, CHF, Shock	PED	2	4	Extensive	5	16	MOF, shock
DM	COPD, Pneumonia	VS, diffuse slowing	1	4	Extensive	5	31	MOF, shock
IA	Mediastinitis	VS	1	3	Extensive	5	22	MOF, shock
NA	Mesothelioma, CPA after biopsy	PED	1	3	Extensive	4	>90	-
EV	CPA after nasoplasty operation	PED	1	1,3	Extensive	4	>90	-
AC	AMI	VS	4	5	Extensive	4	>90	-
MC	AMI	Not done	-	22	Regional (B-hippocampal)	2	>90	-
Nes	Pneumothorax, CHF, MCA Stroke 3 months ago	Diffuse slowing	2	6	Normal, old MCA and small embolic infarcts	5	16	Weakened on day 5 (GCS:9), But died from cardiogenic shock
AO	Mesenteric occlusion, amyloidosis	VS, diffuse slowing	6	12	Regional, (B-pallidal and occipital)	5	42	Reached to GCS of 14, but died of MOF later.
SB	AVR, Endocarditis with abscess and thrombus	Not done	-	4	Regional (B-striatal and occipital infarct, left occipital hemorrhage)	5	9	Weakened on day 3, But died from cardiogenic shock
OK	COPD, CHF	VS, diffuse slowing	2	9	Regional (B-mesial temporal +hippocampal)	3	>90	-
DC	s/p CABG-MVR	VS, diffuse slowing	10	8	Regional (B-occipital infarcts, Multiple embolic lesions)	5	17	Weakened to a CPC category 1, but died of recurrent cardiac arrest later

Notes—ID refers to initials of the name of each patient; DM indicates diabetes mellitus; CAD, coronary artery disease; PTE, pulmonary thromboembolism; AMI, acute myocardial infarction; ARF, acute renal failure; s/p, status post; CABG, coronary artery bypass grafting; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CPA, cardiopulmonary arrest; AVR, aortic valve replacement; MVR, mitral valve replacement; BSP, burst suppression pattern; VS, voltage supression; PED, periodic epileptiform discharges; EEG, electroencephalography; MRI, magnetic resonance imaging, B-,bilateral; CPC, cerebral performance category; MOF; multi-organ failure; GCS, Glasgow coma scale.

Table 2. Comparison of Clinical and Laboratory Data

Prognosis	CPC 4 or 5	CPC 1,2 or 3	
N	16	6	p-value
Age	54±18	63±12	p=0,178
Female/Male	6/10	2/4	p=0,590
Arrest Place (Out of-/In-hospital)	7/9	0/6	p=0,067
CPA type (CP/PC)	12/4	2/4	p=0,096
CPR initiation time (>5/<5 minutes)	8/8	1/5	p=0,178
CPR duration*	25±25 (20)	15±15 (10)	p=0,367
CPR duration (>20 / <20 minutes)	7/9	4/2	p=0,318
GCS visual*	1,3±0,5 (1)	2,3±0,8 (3)	p=0,010
GCS verbal	-	-	-
GCS motor*	2,0±1,1 (2)	4,3±0,5 (4)	p=0,001
GCS total*	4,2±1,4 (4)	7,7±1,2 (8)	p=0,001
FOUR visual*	0,3±0,4 (0)	1,3±0,8 (1,5)	p=0,010
FOUR brainstem*	3,8±0,7 (4)	3,7±0,8 (4)	p=0,914
FOUR respiratory*	0,4±0,5 (0)	0,8±0,8 (1)	p=0,231
FOUR Motor*	0,9±0,9 (0)	2,3±0,5 (2)	p=0,003
FOUR Total*	5,3±1,6 (5)	8,2±2,2 (8)	p=0,008
Upward eye deviation (+/-)	4/12	0/6	p=0,249
Myoclonic status epilepticus (+/-)	3/13	0/6	p=0,364
First EEG time*	4,5±5 (2) (n=13)	5±4 (4) (n=4)	p=0,549
EEG-malignant patter (+ / -)	6 / 7 (n=13)	0/4 (n=4)	p=0,139
MRI time*	4,1±2,9 (3,5)	9,8±5,7 (8,5)	p=0,040
Second MRI time	5,3±3,6 (4) (n=4)		
MRI extensive lesion pattern (+/-)	14/2	0/6	p<0,001

Notes—CP indicates first cardiac, which followed by pulmonary arrest; PC: First pulmonary and then cardiac; CPA: cardiopulmonary arrest; CPR: cardiopulmonary resuscitation; GCS, Glasgow coma scale; EEG, electroencephalography; MRI, magnetic resonance imaging. *: mean±SD, numbers in brackets represent median.

diffuse cortical pattern of MRI abnormality may, therefore, be a radiographic signature of poor neurological outcome after CPA.

Extensive cortical lesion pattern represents bilateral and symmetrical gyriform involvement usually in most portions of the occipital, parietal and frontal lobes as evaluated by increased FLAIR or DWI signal accompanied by swelling especially in the subacute phase of PRE. The occipital lobes were affected in almost all patients. The underlying mechanism of this lesion distribution is suggested to be cortical laminar necrosis. Microvacuolation which is suggested as the initial phase of cortical laminar necrosis may reflect the high sensitivity of DWI through diffusion restriction. Because of its capability to detect restricted water diffusion (22), DWI is sensitive enough to detect an abnormality in the first hours after CPA, although patients are rarely imaged this early. In this acute period, cerebral cortex is usually affected in isolation. Involvement of the thalamus, basal ganglia and cerebellum in addition to cortex is more frequently seen in scans obtained later after CPA (11, 23), but can be present in some patients with severe PRE. Cortical involvement is easily detectable by DWI between 1 and 7 days after CPA, after which pseudo-normalization of ADC may occur. On the other hand, FLAIR images that could be evaluated as normal on inspection in cases of mild cortical signal increase without expansion in the acute phase of the episode are apparently abnormal in the subacute period (4, 5). No white matter abnormalities, denoting ischemic myelinopathy with cytotoxic edema histologically, is seen on scans performed earlier than 72 hours (5, 11, 24). During the chronic phase, diffuse atrophy and related dilatation of the ventricles are visible (23).

It is important to know that no fixed pattern of MR imaging abnormality in patients with PRE was present. In addition to the aforementioned typical widespread cortical involvement, other various patterns of MR imaging abnormalities after CPA have been described (9, 10, 12, 24). First of all, the MRI lesion pattern is clearly different in patients with pulmonary arrest without subsequent systemic perfusion failure (hypoxic hypoxia) (9). Hippocampus, medial temporal lobes and basal ganglia are more vulnerable in this kind of arrest. In some patients, selective pallidal necrosis produces a peculiar, but nonspecific, appearance termed, the “eye of the tiger.” We observed these hypoxic patterns in three patients; two patients with primary pulmonary arrest followed by a very brief circulation cessation and one patient with cardiac arrest. The two patients survived by having CPC category 2 and 3, and the third patient died of systemic causes. Wernicke’s encephalopathy-like lesions observed in another patient have been recently reported in conjunction with PRE (25). Gyral edema and scattered sulcal hyperintensity representing protein extravasation into the subarachnoid space, also described previously (4), was present in one patient of our series. There were also coincidental embolic infarcts and lobar hemorrhages in the same patient.

Several important issues should be mentioned before declaring brain MR imaging as a valuable prognostic tool in

Table 3. ROC Curve Analysis

	ROC AUC	Criterion	Sensitivity (95% CI)	Specificity (95% CI)	+LR	-LR
GCS Eye	0,854±0,105 (0,639-0,965)	<=1	75,0 (46,6-92,6)	83,3 (36,1-97,2)	4,50	0,30
GCS Motor	0,958±0,060 (0,776-0,992)	<=3	87,5 (61,6-98,1)	100,0 (54,1-100,0)	-	0,13
GCS Sum	0,953±0,063 (0,769-0,993)	<=5	81,2 (54,3-95,7)	100,0 (54,1-100,0)	-	0,19
FOUR Eye	0,854±0,105 (0,639-0,965)	<=0	75 (47,6-84,7)	83,3 (36,1-97,2)	4,50	0,30
FOUR Brainstem	0,521±0,140 (0,301-0,735)	>2	87,5 (61,6-98,1)	16,7 (2,8-63,9)	1,05	0,75
FOUR Respiratory	0,677±0,137 (0,447-0,857)	<=0	62,5 (35,5-84,7)	66,7 (22,7-94,7)	1,87	0,56
FOUR Motor	0,896±0,091 (0,691-0,982)	<=1	68,7 (41,4-88,9)	100,0 (54,1-100,0)	-	0,31
FOUR Sum	0,859±0,104 (0,645-0,967)	<=7	87,5 (61,6-98,1)	66,7 (22,7-94,7)	2,62	0,19
Up deviation	0,625±0,131 (0,396-0,819)	Present	25,0 (7,4-52,4)	100,0 (54,1-100,0)	-	0,75
MSE	0,594±0,134 (0,366-0,795)	Present	18,8 (4,3-45,7)	100,0 (54,1-100,0)	-	0,81
EEG	0,808±0,106 (0,556-0,950)	Malignant	61,5 (31,6-86,0)	100,0 (48,0-100,0)		0,38
MRI	0,937±0,051 (0,746-0,992)	Extensive	87,5 (61,6-98,1)	100,0 (54,1-100,0)	-	0,13

Notes—ROC indicates receiver operator characteristics; AUC, area under curve; CI, confidence intervals; +LR, positive likelihood ratio; −LR, negative likelihood ratio; GCS, Glasgow coma scale; EEG, electroencephalography; MRI, magnetic resonance imaging, MSE, Myoclonic status epilepticus.
Numbers are given as mean±standard error, numbers in brackets represent 95% confidence intervals.

this setting. First of all, there are some potential technical pitfalls associated with MR imaging in this specific indication (11). Because of the diffusivity of signal changes especially when subtle in the very early stage imaging abnormalities may be missed if images are not viewed under proper windowing of image contrast (12). Secondly, albeit the severity of neurological involvement is important; the mortality rate in PRE actually mirrors the mortality rate of the primary disease. Since the underlying diseases have a high mortality and morbidity rates, studies testing the place of MR imaging in this indication are prone to error. Third, the effect of therapeutic hypothermia in patients with different involvement patterns in MR imaging remains obscure. Furthermore, no controlled studies of a large number of patients regarding MR imaging findings in PRE patients have been reported. Since MR imaging findings cannot be used to guide treatment limitation decisions on the basis of few isolated case reports and small series appearing in the literature, prospective controlled studies using early and serial MR examinations are necessary to clarify its prognostic utility. This is especially true for considering therapeutic hypothermia. We found that AUC of ROC of MR imaging is significant (0.937). However, the lower limit of the specificity is only 54.1% referring to a high false positive rate (FPR: "1-specificity"). FPR is the most appropriate parameter for the clinicians who want to have prognostic information with a high level of certainty (low FPR). Finally, our findings in this study reveal that incorporation of radiological and clinical data results in a clear increase of sensitivity but not in specificity. In contrast, making decisions seems to be easier in PRE patients with normal MR imaging findings. An aggressive management strategy may be suggested in patients who have normal MR imaging irrespective of neurological function on the initial clinical examination. Although there are clear advantages for procedural safety and easiness, brain CT seems to be not sensitive enough for providing prognostic information compared to MRI in our series. Even though our study was not directed to compare the utility of these two imaging modalities, brain CT, when obtained, showed significant edema in only 28% of patients with a poor prognosis.

All in all, we think that sedative and paralytic medications, which are commonly used in CPA survivors, may make the interpretation of the neurological examination find-

ings impossible especially during the early period after CPR. DWI and FLAIR imaging may help overcome this problem. When treating physicians and family members require more information on prognosis, MR imaging could be a useful modality. However, the potential of MRI to complement examination-based predictions of outcome and to select target populations most likely to benefit from treatment strategies needs further study.

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