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MRI brain lesion patterns in patients in anoxia-induced vegetative state

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Abstract

The object of this study was to analyze magnetic resonance imaging data from patients with disorders of consciousness who were suffering from non-traumatically induced brain lesions with respect to the pattern of vulnerability and to examine the associations between the sizes of these lesions and the clinical outcome of the patients. To this end, T1- and T2-weighted brain images were examined in twelve patients in the post-anoxic vegetative state after a median of 21 days after the causative event. Predominant in the characteristic lesion patterns were regions of pathological white matter signals within the frontal and occipital lobes and in the periventricular regions. The total volumes of the lesions were found to be associated with the severity of the patients' clinical outcomes as measured by the Ranchos Los Amigos Cognitive Scale after a median of 25 months. These lesion patterns demonstrated damage to cerebral networks critical to higher cognitive processes ("consciousness") in both white and gray matter. The relevance of these findings for patients in anoxia-induced decreased levels of consciousness is discussed.

Keywords: Anoxia; Magnetic resonance imaging; Vegetative state; White matter lesions

1. Introduction

The cerebral correlates to human consciousness remain topics of intense discussion and controversy [1,2]. Survivors of severe traumatic or hypoxic brain damage who are initially comatose usually pass through a spectrum of clinical conditions before partially or fully recovering consciousness. If, after having been in a coma, the patient opens her or his eyes but remains unable to initiate voluntary motor activity, this marks the transition to the vegetative state (VS); the further transition to minimally conscious state (MCS) is marked by reproducible evidence of (simple) voluntary behaviour, whereas emergence from MCS is signaled by the return of functional communication or object use. Further developments lead to outcomes ranging from severe disability to a good recovery [3]. If, however, the patient remains in the VS for more than one month after the occurrence of brain damage, this condition is called the "persistent VS" (PVS). This state is not necessarily irreversible. Reversibility is much less likely in patients in the "permanent VS", i.e. in a VS lasting more than 3 months after non-traumatic or 12 months after traumatic brain injury [4,5]. The prognosis of patients in the VS/PVS due to cerebral anoxia has generally been considered to be particularly grave, but has been shown to be reversible in rare cases [4–8].

Over the past years, multiple investigations using electrophysiological, nuclear medical, and functional magnetic resonance imaging (fMRI) techniques have shown that, contrary to earlier expectations, patients with severe disorders of consciousness (PVS, MCS) respond to a variety of stimuli

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with cerebral cortical activity ([9–14]]; cf. [15] for a review). It can, however, be argued that all these activation paradigms map neural activity reflecting automatic processing rather than demonstrating conscious awareness [16]. The use of paradigms during which subjects are instructed to remember or imagine well-defined mental actions, as suggested by Owen and co-workers [17], might reflect volitional neural activation only in cases that yield particularly robust specific findings in individual subjects. Certainly negative findings in such a paradigm do not exclude awareness. The application of the advanced imaging techniques necessary to employ this paradigm (the employment of which is further complicated by idiosyncracies of this difficult-to-investigate patient population) has generally been limited to specialized centers and thus most patients, world-wide, who are in the VS or PVS remain untested by these criteria.

The contribution of structural conventional MRI to this discussion has been minor up to now. The few MRI studies which describe lesions caused by global cerebral damage of a non-traumatic origin present heterogeneous findings and do not consider the PVS as a separate outcome group [18,19]. After early autopsy studies which have been summarized by Kinney and Samuels [20], post-mortem aspects of the brain lesions of patients who had suffered from non-traumatic PVS have been investigated by Adams and co-workers [21]. They reported that brains of these patients exhibit massive damage of the gray matter both diffusely and focally, particularly in the neocortex and the thalamus, and widespread damage of the white matter, with consecutive atrophy and ventricular enlargement. In the present retrospective study, MRI findings from a group of patients who were in the VS/PVS after non-traumatic brain injury (cerebral anoxia) and belonged to different outcome classes were scrutinized, in order to investigate the MRI lesion pattern and size *in vivo*, in correlation with the clinical outcome after a follow-up period of a median of 25 months.

2. Patients and methods

Twelve patients were examined (8 males, 4 females; age range 37–73 years, median 52 years) who suffered from global cerebral anoxic damage caused by primary respiratory or cardiac arrest (for clinical features, cf. Table 1). Patients in whom cardiac/respiratory arrest was due to states directly involving the central nervous system (subarachnoid haemorrhage, encephalitis, and intoxication) and patients with previous brain lesions or a previous history of drug or alcohol abuse were not included. We also excluded patients who had developed secondary neurological complications after the anoxic event (e.g. shunt infection) which might have influenced the MRI data or the clinical outcome.

The diagnosis of the PVS was made according to the criteria of the Multi-Society Task Force [4,5] by two independent neurologists who were unaware of the MRI findings. All patients were examined weekly by two expert neurologists, and all patients had been first in a state of coma and had then developed into the VS. The durations of coma and VS/PVS and the transition to further recovery were defined clinically by the generally accepted criteria as outlined in the Introduction [3,16]. Coma had lasted between 6 and 55 days (median 21 days) (Table 1). MRI was performed after a minimum of 37 days after the causative event. At the time of scanning, the patients were either in the VS ($n=3$; patients 1, 7, 10), in the PVS ($n=7$; patients 2, 4, 6, 8, 9, 11, 12) or in an early remising state, i.e. MCS ($n=2$; patients 3, 5). The time spans between causative event and MRI scanning are also listed in Table 1.

MRI scans were acquired with a standard clinical 1.5 Tesla MR tomograph (Gyroscan®, Philips Medical Systems, Best, Netherlands). Anatomical MRI included axial T1-weighted spin echo images (18 slices, 6 mm thickness, 2 mm gap, field of view (FOV) 190 mm, matrix 256, repetition time (TR) 500 ms, time to echo (TE) 12 ms), axial T2-weighted turbo spin echo images (18 slices, 6 mm thickness, 2 mm gap, FOV 190 mm, matrix 256, TR 2000 ms; TE 100 ms), and corresponding axial fluid attenuated inversion recovery (FLAIR) images (18 slices, 6 mm thickness, 2 mm gap, FOV 190 mm, matrix 256, TR 9000 ms; TE 118 ms). The white matter lesion volume was evaluated in the axial FLAIR images by using a manual region of interest delineation by an experienced neuroimaging researcher and a volume of lesion calculation within the MRIcro® software package (http://www.sph.sc.edu/comd/rorden/mricro.html) [22]. Lesions were classified as having been present in the gray and/or white matter in four different brain regions (frontal, parietal, temporal, occipital). An additional separate evaluation was performed for the basal ganglia, thalamus, hippocampus, cerebellum, and brainstem.

The total clinical follow-up period of all patients from the time of the causative event lasted for at least 5 months (between 154 and 5200 days, median 738 days) (cf. Table 1). One patient (No. 3) died after 7 months due to a second myocardial infarction. The clinical outcomes were reported according to the Rancho Los Amigos Cognitive Scale (RLACS) [23] as a universal guide to assess a patient's level of functioning. The eight levels of outcome on this scale range from I="no response" to VIII="purposeful, appropriate response". The final rating of each patient was done during the period of clinical follow-up.

According to this clinical scale, the 12 patients were divided into three outcome classes (cf. Table 1):

Class 1 RLACS levels VII–IV: conscious but severely disabled patients (patients 1–3),
Class 2 RLACS level III (localized response): MCS (patients 4–7),
Class 3 RLACS level II (generalized response): PVS (patients 8–12).

The final RLACS levels were correlated to the MRI lesion size with a Spearman correlation as implemented in the

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Table 1
Clinical features of the patients (in order to clinical outcome, first=best)

No.	Age/ sex	Aetiology of cerebral hypoxia	MRI		Coma [days] [a]	VS [days] [a]	Follow-up [days] [a]	Outcome RLACS [b]	Outcome class
			[days] [a]	Lesion [mm^3]					
1	39/M	Cardiac arrest of unknown origin	50	153,990	30	62	508	VII	1. Conscious but disabled
2	49/F	Hypovolemic shock	60	318,850	13	47	2950	V	
3	62/M	Myocardial infarction	90	115,590	18	45	210	IV †, 7 months	
4	61/M	Myocardial infarction	79	279,580	28	150	370	III	2. Minimally conscious state
5	42/M	Diving accident	4,000	255,100	30	3300	5200	III	
6	51/M	Myocardial infarction	705	805,130	6	730	216	III	
7	63/M	Myocardial infarction	37	225,270	20	120	450	III	
8	37/F	Cardiomyopathy	60	700,810	15	pers. [c]	154	II	3. persistent vegetative state
9	73/F	Pulmonar embolia	96	531,810	22	pers.	2100	II	
10	59/F	Asthma attack	70	401,840	55	pers.	1050	II	
11	43/M	Asthma attack	152	700,810	35	pers.	967	II	
12	53/M	Hypoxia during surgery	58	477,720	18	pers.	1080	II	

[a] Time between the event and the MRI, duration of deep coma, duration of vegetative syndrome and time between event and last follow-up investigation in days.
[b] Rancho Los Amigos Cognitive Scale; levels of cognitive functioning.
[c] pers.: persisting.

Statistical Package for the Social Sciences (SPSS 10.05, Chicago, IL, USA).

3. Results

The distribution of the MRI findings is summarized in Table 2. All findings with respect to lesions were, to a large extent, symmetrical, so that the results are reported for both hemispheres together. All patients (except from patient 3) exhibited cortical lesions of some degree, generally most pronounced in the frontal and occipital lobes. The patients with the worst outcomes (outcome class 3) showed a more widespread lesion pattern of cortical lesions, whereas the patients with better outcomes (class 1) showed only minor cortical damage. All 12 patients exhibited white matter lesions to some degree in at least two regions, involving the white matter adjacent to the primary motor area (precentral gyrus), in the occipital lobe, typically following the optic radiation, and in periventricular regions– particularly in the frontal or parietal areas– but also in temporal regions. In essence, the FLAIR images revealed a band of signal hyperintensities following the borders of the lateral ventricles in all patients (parietal, temporal and frontobasal lobes). The distribution of the compromised white matter areas did not correspond to the vascular watershed. Global supratentorial brain atrophy was evident in all patients; in two cases it was particularly pronounced.

The hippocampus was involved in 11 of the 12 patients. Lesions in the basal ganglia were present in 11 patients,

Table 2
MRI features of the patients (in order of clinical outcome; first=best)

No.	Gray matter/cortex [a]				White matter [b]				BG [c]	TH [c]	HC [c]	CB [c]	BS [c]	Atrophy [d]
	Frontal	Parietal	Temporal	Occipital	Frontal	Parietal	Temporal	Occipital						
1	+	0	0	+	+	0	0	+	+	+	0	0	0	+
2	+	0	0	0	+	0	0	+	+	0	+	0	0	+
3	0	0	0	0	+	0	+	+	+	0	+	0	0	++
4	+	0	0	0	++	+	0	+	+	+	+	+	0	+
5	+	0	+	++	++	+	0	++	0	+	+	+	0	++
6	+++	++	+++	+++	+++	++	+++	+++	+	+	+	+	+	+++
7	++	0	0	0	++	+	0	+	+	0	+	0	0	++
8	0	++	0	++	+++	+	0	+++	+	+	+	0	0	++
9	+++	++	+++	+++	+++	++	++	+++	+	0	+	+	+	++
10	++	0	0	+++	++	+	0	+++	+	+	+	0	0	++
11	++	++	++	+++	+++	+	+	+++	+	+	+	+	+	+++
12	+++	0	0	0	+++	+	0	+++	+	0	+	0	0	+

[a] Cortex: cortical lesion; 0: not visible; +: involves less than 2 gyri adding up right and left side; ++: less than 4 gyri adding up right and left side; +++: involves more than 4 gyri.
[b] White: white matter lesion; 0: not visible; +: involves less than 1/3 of the whole white matter of the present lobe adding up right and left side; ++: involves more than 1/3 but maximum 2/3 of the whole white matter of the present lobe adding up right and left side; +++: involves more than 2/3 of the whole white matter of the present lobe.
[c] Additional regions, BG: basal ganglia; TH: thalamus; HC: hippocampus; CB: cerebellum; BS: brainstem; 0: no; +: lesion.
[d] Supratentorial atrophy: 0: no atrophy; +: slight; ++: moderate; +++ severe; all with respect to age.

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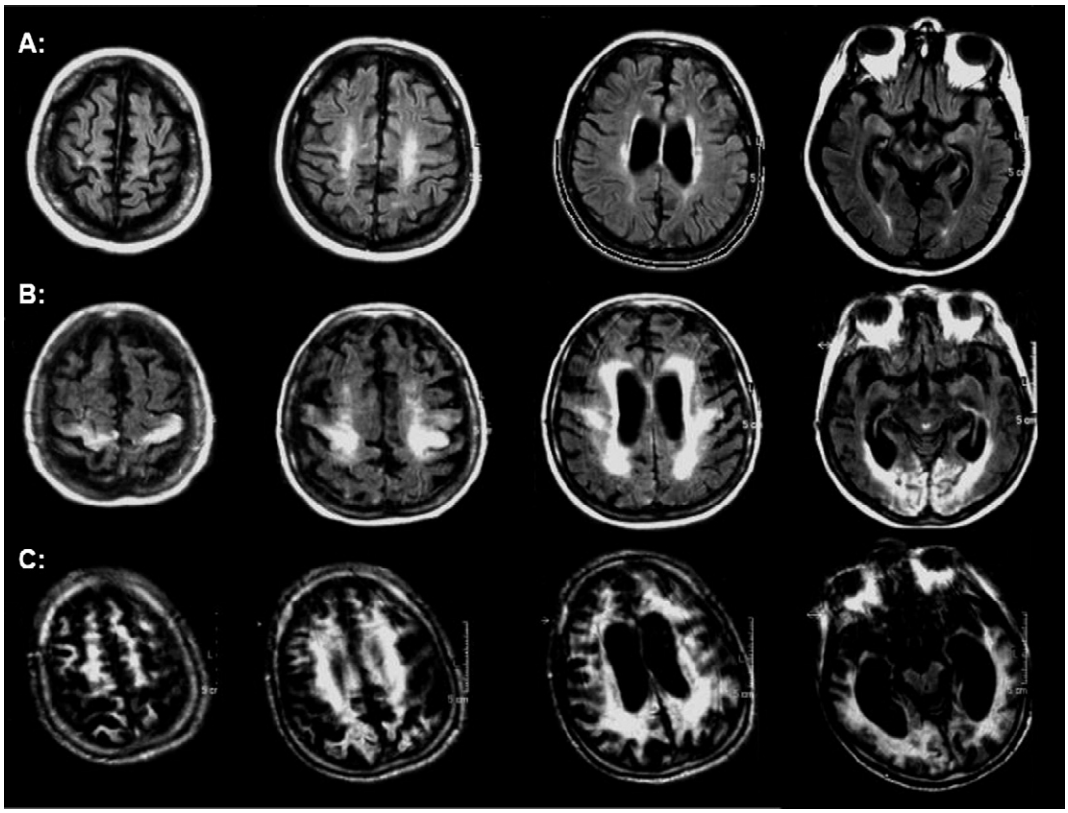

Fig. 1. Representative examples of single subjects. A: Lesion group 1; predominant periventricular white matter lesions and some lesions around the primary motor and visual cortex. B: Lesion group 2; larger lesions in the same areas as detected in group 1. C: Lesion group 3; signal hyperintensities of the entire occipital lobe, within the upper frontal lobe and around the (enlarged) ventricular system, expanding at the level of the frontal horn and around the occipital part of the trigonum.

usually with hyperintensities (T1-weighted image) in the putamen and pallidum, but occasionally also in the caudate. Thalamic lesions were observed in 7 patients. The brainstem was involved in 3 patients, and the cerebellum was damaged in 5 patients.

The size of the white matter lesions varied from patient to patient. At the least, a region of signal hyperintensity on the FLAIR weighted images was limited to the occipital or parietal lobe and to a slim periventricular band (patients 1–3) (Fig. 1A). An intermediate finding was represented by larger lesions in the same regions (patients 4, 5, 7; Fig. 1B). The largest lesions (patients 6, 9, 12) consisted of a signal hyperintensity of the most part of the occipital lobe, an extended region of the upper frontal lobe and an extended periventricular band involving all cerebral lobes, expanding to the level of the frontal horn and/or around the occipital part of the trigonum (Fig. 1C). In these severe cases, lesions also reached into the parietal lobe, the upper temporal lobe and the frontobasal gyri.

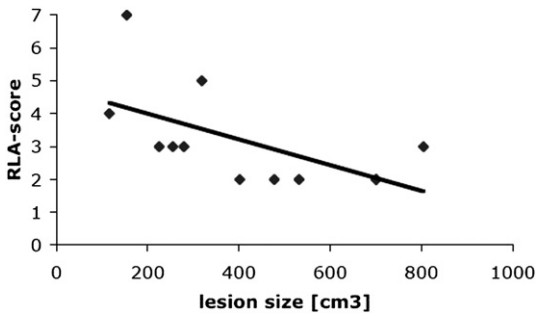

Fig. 2. Plot of lesion size against clinical outcome as assessed by the RLAS ($r=-0.68$; $p<0.01$).

Whereas the lesion volumes added up to a median of 154 cm^3 in the brains of the patients with outcome class 1, the lesion volumes in the brains of patients belonging to outcome class 2 showed a median of 267 cm^3. The lesion volumes of the brains of patients belonging to class 3 showed a median volume of 532 cm^3. The individual white matter lesion volumes are included in Table 1. The global white matter lesion volume correlated negatively with the RLACS ($r=-0.68$; $p<0.01$) (Fig. 2).

4. Discussion

This study of patients with severe disorders of consciousness after an event of prolonged cerebral hypoxia (VS/PVS) identified a characteristic pattern of brain lesions in MRI. All patients demonstrated extensive white matter lesions, with the largest lesions observed in the frontal and occipital lobe. Lesion magnitude showed an association with the severity of the outcome as quantitatively assessed by RLACS.

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Previous MRI-based *in vivo* studies of patients who were in a long-term state of disturbed consciousness of non-traumatic origin are rare and mostly casuistic reports. Most previous studies focused on the early detection of pathological findings soon after the anoxic event. An investigation by Arbelaez et al. [24] using diffusion-weighted imaging (DWI) demonstrated that gray matter abnormalities were observed on DWI during the early subacute period and that DWI showed mostly white matter abnormalities during the late subacute period. A DWI study in patients in acute stages after cerebral hypoxia [25] showed that pathological DWI during the early phase after cerebral hypoxia might be superior to MRI as a predictor of an unfavorable clinical outcome. In addition, a region-of-interest-based analysis of high-*b*-value DWI performed by Tha et al. [26] demonstrated alterations already visible in the early stage (<24 h) of global cerebral anoxia.

The aim of the present study was to define a pattern of spatial distribution and a magnitude of the signal changes and to investigate the association of those parameters with the various outcomes of patients in the VS/PVS. According to the literature, lesions of the cerebral white matter are considered to be less common in post-anoxic cerebral damage [18,27]. Gray matter lesions have generally been considered to be more common. This prevalence has been interpreted to be the result of the higher energy demand [27] of gray matter and/or the higher density of glutamate receptors found in gray matter areas [20]. Moreover, the majority of functional neuroimaging studies done up to now have addressed the question of whether neocortical functions were at least partly preserved, i.e. it has been the gray matter segment that has been considered to be the most relevant brain compartment to be studied. The only computerized automatic analysis of structural volume-rendering T1-weighted MRI in PVS patients to date, using voxel-based morphometry, also aimed at analyzing the gray matter segment [28]; the authors demonstrated multilocal structural loss involving both parietal lobe (inferior aspects), frontal lobe (superior and medial areas), and temporal lobe (superior and medial areas), and, in addition, losses in the cingulate and the fusiform gyrus. Recent post-mortem studies in humans, however, have indicated a high degree of vulnerability of the white matter in cases of ischemic–anoxic insults [20,21]. Taking these findings into consideration, we specifically investigated both gray and white matter structural damage in our approach. The finding of a high degree of overlap between cortical and white matter lesions was remarkable and in accordance with the above-named autopsy studies. Furthermore, the widespread white matter lesions followed a typical spatial distribution inasmuch as they always involved the subcortical areas adjacent to primary motor area and to primary visual cortices, furthermore the directly periventricularly localized areas. Other white matter regions, however, in particular within the parietal and the upper temporal lobes were frequently spared.

This finding of a relatively uniform involvement of particular areas as described above is striking, since it was observed despite the quite heterogeneous medical histories of the patients described here, suggesting a selective vulnerability of the brain regions involved, independent of the individual aetiology. Some of the vulnerable white matter regions described in literature belong to the so-called "vascular watershed" areas, but some were not as for instance the periventricular areas [27,29]. With respect to gray matter lesions, the vulnerability pattern observed included frontal and occipital and in some cases parietal cortical areas, moreover in most cases the thalamus. Additionally, almost all of our patients showed lesions of the hippocampus or lesions to the basal ganglia (11/12 patients). These data are supported by the post-mortem data; especially the thalamus is well known to be severely damaged after global hypoxia. This damage to the thalamus seems to be functionally very relevant inasmuch as, (1) it has been described as one key factor in the occurrence of PVS, (2) thalamic changes were sometimes the most prominent finding at autopsy [20], and (3) thalamic lesions located in the nuclei preferentially connected via white matter fibers with particular cortical association areas that are known to result in functional damage similar to that after a lesion of the cortical region itself. The pathophysiological reasons for the vulnerability of the white and gray matter areas which have been damaged in these patients must remain speculative at present.

We found an association between the extent of the MRI-defined lesions located within the white matter (Table 2) and the clinical outcomes of the patients (cf. Table 1 and Fig. 2). All patients in the most unfavorable class III clinical outcome group exhibited white matter lesions exceeding 2/3 of the volume of at least one lobe, most frequently the occipital lobe. The particular role of strategic areas important for the integrity of cerebral connectivity and the complex function of consciousness are well established. However, the correlational analysis within the cross-sectional design of this study did not allow for a statement on the predictive potential of MRI alterations (including white matter volume changes) in PVS, but only provided an index of association. For an analysis if MRI findings might predict the clinical outcome, a (prospective) study in a longitudinal design with serial MRI scanning would be required.

These insights into the general pathoanatomy of patients with disorders of consciousness, in particular the lesion pattern especially within the white matter, will further improve our understanding of the complex cortical network essential for conscious behavior. The sample size of $N=12$, together with the factor of the interindividual heterogeneity in PVS *per se*, cautions against too generalized conclusions so that the results of the present study have to await confirmation in future studies in a prospective design with a larger sample size of patients.

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