Original article

Voxel-based statistical analysis of cerebral glucose metabolism in patients with permanent vegetative state after acquired brain injury

Yong Wook Kim, Hyoung Seop Kim, Young-Sil An and Sang Hee Im

Keywords: *cerebral glucose metabolism; permanent vegetative state; acquired brain injury*

Background Permanent vegetative state is defined as the impaired level of consciousness longer than 12 months after traumatic causes and 3 months after non-traumatic causes of brain injury. Although many studies assessed the cerebral metabolism in patients with acute and persistent vegetative state after brain injury, few studies investigated the cerebral metabolism in patients with permanent vegetative state. In this study, we performed the voxel-based analysis of cerebral glucose metabolism and investigated the relationship between regional cerebral glucose metabolism and the severity of impaired consciousness in patients with permanent vegetative state after acquired brain injury.

Methods We compared the regional cerebral glucose metabolism as demonstrated by F-18 fluorodeoxyglucose positron emission tomography from 12 patients with permanent vegetative state after acquired brain injury with those from 12 control subjects. Additionally, covariance analysis was performed to identify regions where decreased changes in regional cerebral glucose metabolism significantly correlated with a decrease of level of consciousness measured by JFK-coma recovery scale. Statistical analysis was performed using statistical parametric mapping.

Results Compared with controls, patients with permanent vegetative state demonstrated decreased cerebral glucose metabolism in the left precuneus, both posterior cingulate cortices, the left superior parietal lobule ($P_{corrected}$ <0.001), and increased cerebral glucose metabolism in the both cerebellum and the right supramarginal cortices ($P_{corrected}$ <0.001). In the covariance analysis, a decrease in the level of consciousness was significantly correlated with decreased cerebral glucose metabolism in the both posterior cingulate cortices ($P_{uncorrected}$ <0.005).

Conclusion Our findings suggest that the posteromedial parietal cortex, which are part of neural network for consciousness, may be relevant structure for pathophysiological mechanism in patients with permanent vegetative state after acquired brain injury.

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Patients with vegetative state (VS) demonstrate intermittent wakefulness as evidenced by eye-opening or sleep wake cycles, however, they are unaware of themselves or their environment. It means that they fail to produce any purposeful or voluntary behavior in response to auditory, visual, tactile or noxious stimulation and do not demonstrate any sign of language comprehension or expression.[1] According to the Multi-Society Task Force,[2] persistent VS has been defined as a VS remaining 1 month after acute traumatic or non-traumatic brain injury and it implies reversibility. However, VS which is 3 months after non-traumatic brain injury or 12 months after traumatic brain injury may be regarded as a permanent VS and it reflects irreversible injury of impaired consciousness.

In the functional neuroimaging studies for VS, Levy et al[3] first reported that patients with VS showed massive cerebral metabolic dysfunction and these results have been confirmed by many other studies for acute and persistent vegetative state.[4-6] However, there are very few studies that have examined the changes of cerebral glucose metabolism in patients with permanent VS and have assessed the relationship between regional cerebral metabolism and the severity in the decreased level of consciousness in permanent VS. Thus, in this study, we investigated the changes of cerebral glucose metabolism in patients with permanent VS after acquired brain injury (ABI) and evaluated the relationship between the changes of cerebral glucose metabolism and the severity in the impaired level of consciousness using statistical parametric mapping of brain F-18 fluorodeoxyglucose positron emission tomography (F-18 FDG PET) by localization with the automated anatomic labeling.[7]

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Department and Research Institute of Rehabilitation Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea (Kim YW)
Department of Physical Medicine and Rehabilitation, National Health Insurance Corporation Ilsan Hospital, Gyonggi-do, Republic of Korea (Kim HS)
Department of Nuclear Medicine, Ajou University School of Medicine, Suwon, Republic of Korea (An YS)
Department of Rehabilitation Medicine, Jeju National University School of Medicine, Jeju, Republic of Korea (Im SH)
Correspondence to: Sang Hee Im, Department of Rehabilitation Medicine, Jeju National University Hospital, Ara 1 dong, 1753-3, Jeju, ZIP 690-716, Republic of Korea (Tel: 82-64-717-2082. Fax: 82-64-717-1131. Email: dongin32@yahoo.com)

METHODS

Patients

We consecutively recruited 16 patients who suffered from VS after ABI. The inclusion criteria for this study were: VS after acquired brain injury by traumatic or non-traumatic causes; VS which is more than 3 months after non-traumatic brain injury or 12 months after traumatic brain injury. The exclusion criteria were: a history of premorbid neurological disease; a history of premorbid impairment in vision, hearing and motor function. Among 16 patients, 2 patients who suffered from traumatic brain injury were during 6 months after injury, and 2 patients resulted from non-traumatic brain injury were in the 2 months after injury. Overall, 12 patients with permanent VS after ABI were enrolled in this study. For statistical parametric mapping (SPM) analysis, the age-matched 12 normal controls were enrolled. The families of all participants gave informed consent. All procedures were performed with the approval of the Institutional Review Board for Clinical Studies.

Evaluation of consciousness level

Evaluation of consciousness level in all patients was performed by a physiatrist with at least three years of experience in the field. All patients underwent an clinical evaluation for consciousness using JFK-coma recovery scale (JFK-CRS).[8,9] The JFK-CRS, initially described by Giacino et al,[10] has been used to evaluate the level of consciousness of patients during recovery after ABI. The JFK-CRS consists of 6 subscales addressing auditory, visual, motor, oromotor, communication, and arousal processes. Scoring is based on the presence or absence of specific behavioral responses to sensory stimuli administered in a standardized manner. The lowest item on each subscale represents reflexive activity, whereas the highest items represent cognitively mediated behaviors; auditory function scale (0–4 points), visual function scale (0–5 points), motor function scale (0–6 points), oromotor function scale (0–3 points), communication scale (0–2 points), and arousal scale (0–3 points). The summation of each 6 subscale becomes to a total JFK-CRS.

F-18 FDG PET images acquisition

Measurement of cerebral glucose metabolism using brain F-18 FDG PET was performed in all controls and all patients. All subjects were scanned using a GE Advance PET scanner (GE, Milwaukee, Wisconsin, USA) with an intrinsic resolution of 4.8 mm full width at half maximum and simultaneous imaging of 50 contiguous transverse planes with a thickness of 3.3 mm for a longitudinal field of view of 14.5 cm. During PET scanning, all patients were instructed to rest comfortably for 20 minutes with their eyes closed and ears unplugged in a quiet room. Emission scanning started after intravenous injection of approximately 555 MBq of F-18 FDG and continued for 15 minutes. An 8-minute transmission scan was performed using triple Ge-68 rod sources to correct for attenuation. Gathered data were reconstructed in a 128×128×35 matrix with a pixel size of 1.95 mm×1.95 mm×4.25 mm by means of a filtered back-projection algorithm employing a trans-axial 8.5 mm Hanning filter and an 8.5 mm axial Ramp filter.

F-18 FDG PET images analysis

Spatial preprocessing and statistical analysis of F-18 FDG PET images in all controls and all patients were performed using SPM software (SPM2, Institute of Neurology, University College London, UK). The F-18 FDG PET templates for all subjects were created by averaging all F-18 FDG PET images and spatially normalization with the Montreal Neurological Institute (MNI, McGill University, Canada) standard PET template using a nonlinear transformation of SPM2. Spatially normalized images were then smoothed by convolution using an isotropic Gaussian kernel with a 12 mm full width half maximum to increase the signal-to-noise ratio and to accommodate the variation in subtle anatomical structures. The effects of global metabolism were removed by normalizing the count of each voxel to the mean count of the brain (proportional scaling in SPM). After spatial normalization, statistical comparisons between the normal control group and the permanent VS group after ABI were performed on a voxel-by-voxel basis using two sample *t*-test. The corrected height threshold (*P* value) <0.001 and extended threshold (*Ke*) >50 was considered to be statistically significant. Additionally, covariance analysis was performed to identify regions in which decreased level of consciousness measured by JFK-CRS was significantly correlated with decreased regional cerebral glucose metabolism in patients with permanent VS using a single-subject covariate model. Regions reaching an uncorrected *P* value of less than 0.005 were considered significant in the covariance analysis with >50 continuous voxels in cluster size. For visualization of the *t*-score statistics, the significant voxels were projected onto the 3D-rendered brain or a standard high-resolution MRI template provided by SPM2, thus allowing anatomical identification. Anatomical labeling of significant voxels was performed using the automated anatomic labeling SPM toolbox[7] which was based on anatomy provided by the Montreal Neurologic Institute.

RESULTS

The patients group consisted of 7 men and 5 women with mean age 41.7 years (range 24–59 years). The control group consisted of 5 men and 7 women with mean age 45.2 years (age range 38–63 years). There was no significant difference between the two groups with respect to sex, age (*P* >0.05).

Table 1 shows the general characteristics of the patients including sex, age, cause of brain injury, duration of injury, impaired level of consciousness measured by JFK-CRS. Among 12 subjects, 5 subjects were caused by hypoxic damage, 4 cases resulted from cerebrovascular injury, and

Table 1. General characteristics of patients with permanent vegetative state after acquired brain injury

No	Sex	Age	Cause of brain injury	Duration of injury (months)	JFK-coma recovery scale	
					A/V/M/O/C/A*	Total
1	M	43	Trauma	23	A1/V0/M1/O0/C0/A2	4
2	M	29	Trauma	33	A1/V0/M0/O0/C0/A2	3
3	F	57	Cerebrovascular	5	A1/V0/M0/O0/C0/A2	3
4	M	25	Hypoxia	60	A1/V1/M0/O0/C0/A2	4
5	F	24	Hypoxia	6	A1/V1/M1/O1/C0/A2	6
6	F	59	Hypoxia	10	A1/V0/M0/O0/C0/A2	3
7	F	53	Hypoxia	5	A0/V0/M0/O0/C0/A2	2
8	M	55	Cerebrovascular	6	A1/V0/M1/O1/C0/A2	5
9	F	47	Cerebrovascular	4	A1/V1/M1/O1/C0/A2	6
10	M	30	Cerebrovascular	55	A1/V0/M0/O0/C0/A2	3
11	M	27	Hypoxia	42	A1/V0/M0/O0/C0/A2	3
12	M	52	Trauma	14	A1/V0/M1/O0/C0/A2	4

*A/V/M/O/C/A: Auditory/Visual/Motor/Oromotor/Communication/Arousal function scale.

Table 2. Brain areas showing the differences of cerebral glucose metabolism in patients with permanent vegetative state after acquired brain injury compared with normal controls

Glucose metabolism	Side	Area	Coordinate			Z score	Cluster	Voxel level ($P_{corrected}$)
			x	*y*	*z*			
Decrease	Right	Posterior cingulate cortex	0	–40	34	8.93	1490	<0.001
	Left	Posterior cingulate cortex	0	–40	34	8.93	1490	<0.001
	Left	Precuneus	–14	–56	8	6.37	1490	<0.001
	Left	Superior parietal lobule	–34	–70	54	5.49	124	<0.001
Increase	Right	Cerebellum	20	–60	–38	9.81	4637	<0.001
	Left	Cerebellum	–18	–50	–38	8.82	4637	<0.001
	Right	Supramarginal cortex	44	–40	28	6.96	145	<0.001

3 patients caused by trauma. The duration of injury was 21.9 months (range 4–60 months) and mean total JFK-CRS was 3.8 points (range 2–6 points).

Table 2, Figures 1 and 2 show the differences of cerebral glucose metabolism between the patients with permanent VS and normal controls. SPM analysis of F-18 FDG PET images showed that, compared with normal controls, significantly decreased cerebral glucose metabolism in patients with permanent VS was in the left precuneus, the both posterior cingulate cortices, the left superior parietal lobule ($P_{corrected}$ <0.001, Table 2 and Figure 1). In contrast, the both cerebellum and the right supramarginal cortex showed significant increase of cerebral glucose metabolism in permanent VS compared with normal controls ($P_{corrected}$ <0.001, Table 2 and Figure 2). In covariance analysis, decreased level of consciousness was significantly correlated with decreased regional cerebral glucose metabolism in the both posterior cingulate cortices in patients with permanent VS after ABI ($P_{uncorrected}$ <0.005, Table 3 and Figure 3).

DISCUSSION

Maintenance of arousal state was supported by several brainstem neurons that directly project to diffuse cerebral cortices.[11] Therefore, functional decline of diffuse cortical structures may cause reduced awakening. The VS, which is a classic example of an impaired consciousness, is fully aroused, but are unaware of themselves and their environment. They can show automatic reactions like moving eyes, head, and limbs in a meaningless manner, and may even grimace, cry, or smile. Some patients might evolve toward full recovery or remain in the minimally conscious sate,[12,13] where some nonreflexive or nonmeaningful behaviors are shown, but, patients are still unable to communicate. Levy et al[3] reported that overall cerebral metabolism in patients with VS is 40%–50% of the normal value health resting state. Characteristics of the changes in the cerebral metabolism in patients with VS are the significantly decreased metabolism in the polymodal associative cerebral cortices and relatively sparing of metabolism in the brainstem.[6] In permanent VS, which reflects the irreversible impairment of consciousness state, brain metabolism values drop to 30%–40% of the normal range of values.[14] This loss of metabolic function over time had been suggested by the result of progressive Wallerian and trasns-synaptic neuronal degeneration.[15]

The precuneus and posterior cingulate cortex, which is part of posteromedial parietal cortex and part of network for consciousness,[16] has been implicated for the maintenance of consciousness state that is connected with higher association cortices and subcortical structures.[17] Recently, PET studies have demonstrated that the precuneus and posterior cingulate cortex show a profound deactivated metabolism in pathophysiologically altered states of consciousness, such as sleep and hypnosis,[18] pharmacologically-induced general anesthesia,[19] and vegetative state.[20,21] In the previous studies which identified regional metabolic dysfunction in VS compared with the conscious resting state in normal controls, voxel-based statistical analyses of cerebral metabolism showed a systematic metabolic impairment, not in the diffuse cerebral cortices, but in the precuneus and posterior cingulate cortex which are known to the most active "by default" in the resting nonstimulated conditions.[21] Vanhaudenhuyse et al[22] reported that

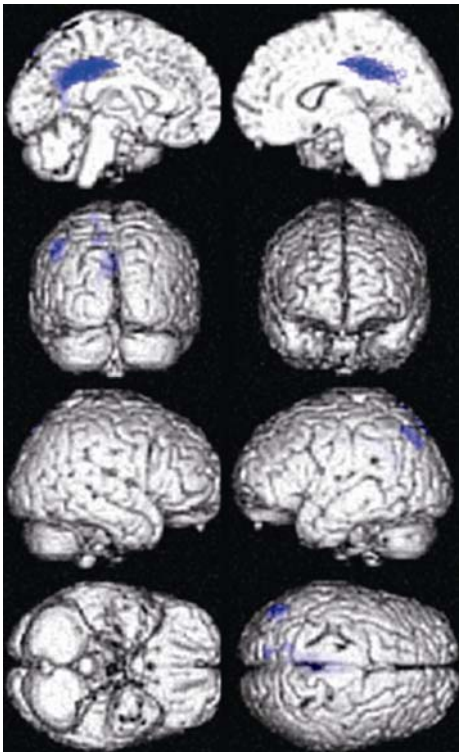

Figure 1. Statistical parametric maps showing spatial distribution of significant decrease of cerebral glucose metabolism in patients with permanent vegetative state after acquired brain injury compared to normal controls. Displayed voxels are significant at P <0.001 after correction for multiple comparisons.

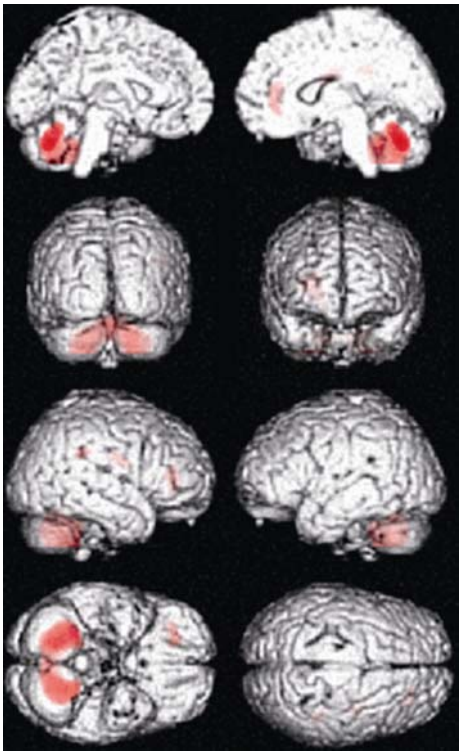

Figure 2. Statistical parametric maps showing spatial distribution of significant increase of cerebral glucose metabolism in patients with permanent vegetative state after acquired brain injury compared with normal controls. Displayed voxels are significant at P <0.001 after correction for multiple comparisons.

connectivity strength within default networks including the precuneus and the posterior cingulate cortex could possibly be a reliable indicator of a patient's level of consciousness, differentiating VS from minimally conscious state in severe brain-injured patients. Our findings also demonstrated that the precuneus and posterior cingulate cortex, which are part of posteromedial parietal cortex, showed significant decrease of cerebral glucose metabolism in permanent VS after ABI. Also, in the covariance analysis, decreased cerebral glucose metabolism in the posterior cingulate cortex was significantly correlated with decrease of consciousness level in patients with permanent VS. Thus, on the basis of our results and those of previous studies, we could speculate the key role of posteromedial parietal cortex in the maintenance of conscious state.

Increased metabolism of the cerebellum in patients with VS has been reported[23] and our results also demonstrated preserved glucose metabolism in the cerebellum. The cerebellum receives mainly afferent inputs from the vestibular system, and the sensory receptors of the extremities and the trunks, and the motor and premotor cortex. Our findings could be hypothesized that relatively preserved input from the body, in contrast to decreased input from the cerebral hemispheres, could lead to a relatively higher neuronal activity of the cerebellum. Rudolf et al[23] reported that the cerebellum is the only brain structure that did not show neural damage in acute VS in contrast to supratentorial cerebral cortex. Also, although the cerebellum may suffer secondary neuronal loss due to transsynaptic degeneration, the cerebellum is primarily spared from the brain injury leading to acute VS.[15] However, our results demonstrated that the cerebellum did not show impaired glucose metabolism reflecting neuronal degeneration previously reported.[15] The underlying mechanism of increased metabolism and the precise role of the cerebellum in patients with permanent VS remain to be elucidated.

Several limitations of the current study design should be considered. First, the sample sizes of the patients with permanent VS in this study were small. Further studies with a larger population are necessary to validate our results. The second limitation relates to the heterogeneous etiology for permanent VS. Because we included all causes of injuries including hypoxic, traumatic and cerebrovascular damages, the findings of study enrolling homogeneous participants should be required in the future study. Also, further study will need to combine metabolic and structural functional neuroimaging studies, such as brain diffusion tensor magnetic resonance imaging, in order to clarify the relationship between metabolic and structural connectivity in permanent VS.

In conclusion, the precuneus and the posterior cingulate cortex, which are part of the posteromedial parietal cortex and part of neural network for consciousness, may be relevant structure for pathophysiological mechanism in

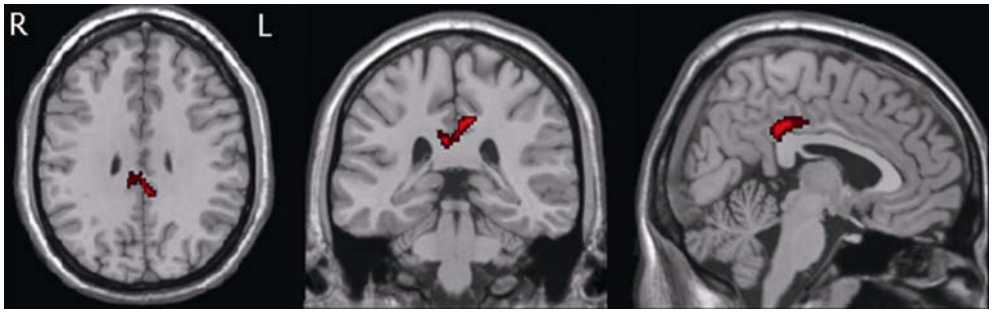

Figure 3. Statistical parametric maps showing correlation of decreased level of consciousness and decreased regional cerebral glucose metabolism in patients with permanent vegetative state after acquired brain injury. Displayed voxels are significant at P <0.005 after uncorrection for multiple comparisons. R: right. L: left.

Table 3. Brain area showing correlation analysis between decreased cerebral glucose metabolism according to decreased level of consciousness

Side	Area	Coordinate			Z score	Cluster	Voxel level ($P_{uncorrected}$)
		x	*y*	*z*			
Left	Posterior cingulate gyrus	–8	–34	36	4.34	145	<0.005
Right	Posterior cingulate gyrus	5	–34	25	4.04	145	<0.005

patients with permanent VS after ABI. A better understanding of the underlying mechanism for permanent VS will contribute to optimizing therapeutic intervention and, consequently can be helpful for the treatment of impaired level of consciousness in patients with permanent VS after acquired brain injury.

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