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Reflex and Spontaneous Movements in Adult Patients during the Process of Determining Brain Death in Korea

Do-Hyung Kim ¹, Oh-Young Kwon ², Tae-Won Yang ³, Minhwa Kim ⁴,
Jeongrim Lee ⁴, Wonhyun Cho ⁴, Jung Sook Yeom ⁵ and Young-Soo Kim ²

¹Department of Neurology, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Korea

²Department of Neurology and Institute of Health Science, Gyeongsang National University Hospital, Gyeongsang National University School of Medicine, Jinju, Korea

³Department of Neurology, Gyeongsang National University Changwon Hospital, Gyeongsang National University School of Medicine, Changwon, Korea

⁴Korea Organ Donation Agency, Seoul, Korea

⁵Department of Pediatrics, Gyeongsang National University School of Medicine, Jinju, Korea

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Address for Correspondence:

Young-Soo Kim, MD, PhD

Department of Neurology, Gyeongsang National University School of Medicine, 79 Gangnam-ro, Jinju 52727, Republic of Korea.
E-mail: youngsookim0127@gmail.com

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ORCID iDs

Do-Hyung Kim
<https://orcid.org/0000-0002-4900-7049>

Oh-Young Kwon
<https://orcid.org/0000-0001-9576-1926>

Tae-Won Yang
<https://orcid.org/0000-0002-8113-2384>

Minhwa Kim
<https://orcid.org/0000-0003-1879-1499>

Jeongrim Lee
<https://orcid.org/0000-0001-6038-5115>

Wonhyun Cho
<https://orcid.org/0000-0001-5916-6601>

Jung Sook Yeom
<https://orcid.org/0000-0003-0688-7493>

Young-Soo Kim
<https://orcid.org/0000-0003-1040-372X>

Disclosure

The authors have no potential conflicts of interest to disclose.

ABSTRACT

Background: Brain death is a clinical diagnosis that implies irreversible loss of function of the entire brain, including the brainstem and both hemispheres. Based on previous reports, it is not rare for reflex and spontaneous movements to occur in patients during the process of determining brain death. However, reports of the frequency and common types of these movements vary from study to study. Thus, we evaluated adult patients with impending brain death in Korea to determine the frequency and characteristics of reflex and spontaneous movements.

Methods: Brain dead patients who were admitted to 15 hospitals in the Yeongnam region (Southeast) of Korea were recruited prospectively from January 2013 to September 2016. All patients met the criteria for brain death as established by the Korea Medical Association. All body movements occurred during the process of diagnosing brain death and were assessed by physicians and trained organ transplant coordinators. The frequency and characteristics of these movements were identified and the demographic and clinical factors of impending brain dead patients with and without these movements were compared.

Results: A total of 436 patients who met the criteria for brain death were enrolled during the study period. Of these patients, 74 (17.0%) exhibited either reflex or spontaneous movements. Of this subset, 45 (60.8%) exhibited reflex movements only, 18 (24.3%) exhibited spontaneous movements only, and 11 (14.9%) exhibited both reflex and spontaneous movements. The most common reflex movements were the flexor/extensor plantar response and spinal myoclonus. Of the 74 patients, 52 (70.3%) exhibited one movement of the same pattern and 22 (29.7%) exhibited two or more different movement patterns. In addition, 45 (60.8%) exhibited these movements only on a limited area of the body with the leg being most common (n = 26, 57.8%). Patients with hypoxic brain damage and a higher systolic blood pressure exhibited significantly more reflex or spontaneous movements.

Conclusion: Movements associated with brain dead patients are not rare and thus an awareness of these movements is important to brain death diagnosis. Physicians who perform brain death examinations should understand the frequency and characteristics of these movements to reduce delays in determining brain death.

Keywords: Brain Death; Reflex; Movement

Author Contributions

Conceptualization: Kim YS. Data curation: Kim M, Lee J, Cho W. Formal analysis: Kim DH, Kim YS. Investigation: Kim M, Lee J, Cho W. Methodology: Kim YS. Validation: Yeom JS. Writing - original draft: Kim DH, Kim YS. Writing - review & editing: Kwon OY, Yang TW.

INTRODUCTION

Reflex and spontaneous movements are not uncommon during the process of determining brain death. The frequency of such movements ranges from 19.2%–75% among all brain dead cases but the reported frequencies widely vary from one study to another.¹⁻⁶ Recently, organ donations from brain dead patients have become common and thus knowledge about such movements is necessary for accurate diagnoses of brain death. Sufficient evidence on how many brain dead patients exhibit reflex or spontaneous movements and whether there are differences in the incidence of these movements according to cause of brain death will aid physicians in correctly diagnosing brain death. Although many studies have investigated the body movements of patients with suspected brain death, few have applied verified tools and neurological tests as a standard protocol for diagnosis.³⁻⁵ In Korea, only a single prospective study of 26 adult brain dead patients at a single tertiary medical center was published in 2006.⁵ Further studies will enhance the current awareness of these movements and might prevent delays and misinterpretations associated with brain death diagnoses. Therefore, the present study assessed 436 brain dead patients in Korea to determine the frequency, characteristics, and factors associated with the presence of reflex and spontaneous movements.

METHODS**Study design**

Brain dead patients who were admitted to 15 hospitals in the Yeongnam region (Southeast) of Korea were recruited prospectively from January 2013 to September 2016 (Fig. 1). Brain death was confirmed by a trained and experienced neurologist, neurosurgeon, or pediatric

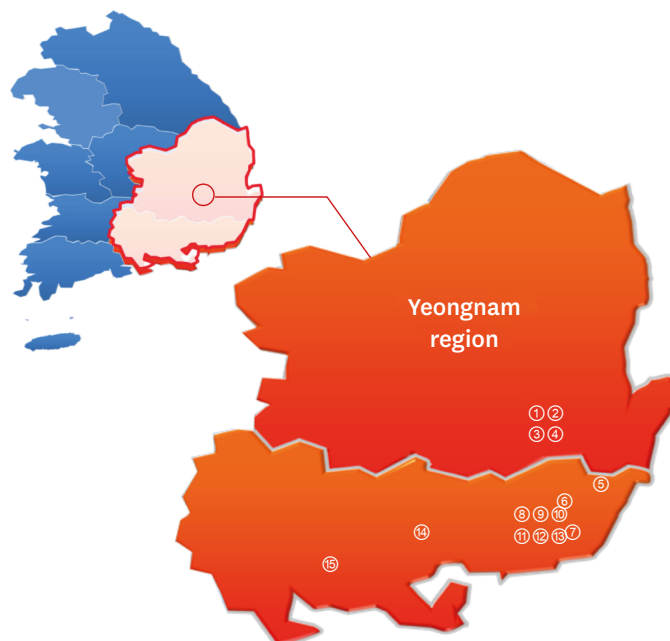


Fig. 1. Yeongnam (Southeast) region and location of the 15 hospitals in Korea. ① Keimyung University Dongsan Medical Center, ② Kyungpook National University Hospital, ③ Yeungnam University Medical Center, ④ Daegu Catholic University Medical Center, ⑤ Ulsan University Hospital, ⑥ Pusan National University Yangsan Hospital, ⑦ Inje University Haeundae Paik Hospital, ⑧ Pusan National University Hospital, ⑨ Kosin University Gospel Hospital, ⑩ Inje University Busan Paik Hospital, ⑪ Bong Seng Memorial Hospital, ⑫ Dong-A University Hospital, ⑬ Changwon Fatima Hospital, ⑭ Samsung Changwon Hospital, ⑮ Gyeongsang National University Hospital.

neurologist according to the guidelines of the Korea Medical Association.⁷ When a physician was making a brain death diagnosis, the organ procurement team (Korea Organ Donation Agency [KODA]) attended the examination and evaluated the patient for reflex and spontaneous movements. If such movements were observed during diagnosis, the patient was enrolled in the present study. All patients included in this study were diagnosed with brain death and completed the organ donation.

Brain death diagnosis and movement provocation protocol

Brain death was determined based on the following guidelines of the Korea Medical Association⁷: complete clinical neurological examination including documentation of coma, the absence of brainstem reflexes, and apnea; exclusion of hypothermia, drug intoxication, and other metabolic causes of coma; and demonstration of electrical inactivity by electroencephalography (EEG) performed after the second examination. The following protocol was performed to provoke movements: painful stimuli applied to the supraorbital area, sternum, and nail beds of the four limbs; neck flexion; tactile stimulation of the palmar and plantar areas; and an apnea test.^{3,4,8} If any movement repeatedly appeared during the process of diagnosis, medical staff members recorded it on video.

Video analyses

Two neurologists described and classified patients' movements by observing video recordings based on previous analyses of known movements.^{6,9,10} Movement was categorized into three groups: reflex movement, which was stimulus-induced only; spontaneous movement, which was present without provocation; and both. The number of movement patterns and the areas where the movements appeared were identified for each patient and categorized as head, neck, body, arm, and leg. Subsequently, the frequency of the movements in the area where they appeared were described.

Analyses of movements without video

A total of 21 cases that lacked video recordings were analyzed based on the physicians' medical records for brain death.

Statistical analyses

SPSS software (version 25.0 for Windows; SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Demographic and clinical characteristics including cause of brain death, hemodynamic parameters, arterial blood gas concentrations, and various medical conditions were compared between the groups. To compare the demographic and characteristic data between the groups, categorical variables were assessed using χ^2 tests and continuous variables were assessed using Student's *t*-tests; *P* values < 0.05 were considered to indicate statistical significance. Forward analyses were applied to significant variables (*P* < 0.05), which were then included in a multiple logistic regression model that controlled for simultaneous interaction factors to generate odds ratios (ORs) and 95% confidence intervals (CIs).

Ethics statement

The study was approved by the Institutional Review Board (IRB) of Gyeongsang National University Hospital (2016-12-018). As the study was a postmortem analysis of data on brain-dead patients, the IRB waived the need for informed consent.

RESULTS

During the study period, 436 adult patients met the criteria for brain death. The demographic and clinical characteristics of the enrolled patients are summarized in **Table 1**.

Causes of brain death

Of the 436 patients enrolled, 132 (30.3%) had traumatic brain injury, 110 (25.2%) had hypoxic brain injury, 95 (21.8%) had subarachnoid hemorrhage, 78 (17.9%) had intracerebral hemorrhage, 14 (3.2%) had ischemic stroke, and 7 (1.6%) had other causes of brain death, including brain tumor, arteriovenous malformation, encephalopathy, and osmotic myelinolysis (**Fig. 2**). Of the 74 (17.0%) patients who exhibited reflex or spontaneous movements, the causes of brain death were as follows: 30 (40.5%) had hypoxic brain injury, 23 (31.1%) had traumatic brain injury, 12 (16.2%) had intracerebral hemorrhage, 8 (10.8%) had subarachnoid hemorrhage, and 1 (1.4%) had ischemic stroke. The causes of brain death in the 362 patients who did not exhibit movement were somewhat consistent with the distribution of the causes of brain death for all patients (**Fig. 2**). However, hypoxic brain injury was more likely to be the cause of brain death among patients with movement than those without movement (univariate analyses, $P = 0.001$; multivariate analyses, $P = 0.001$) (**Fig. 2**, **Tables 2** and **3**).

Reflex and spontaneous movements

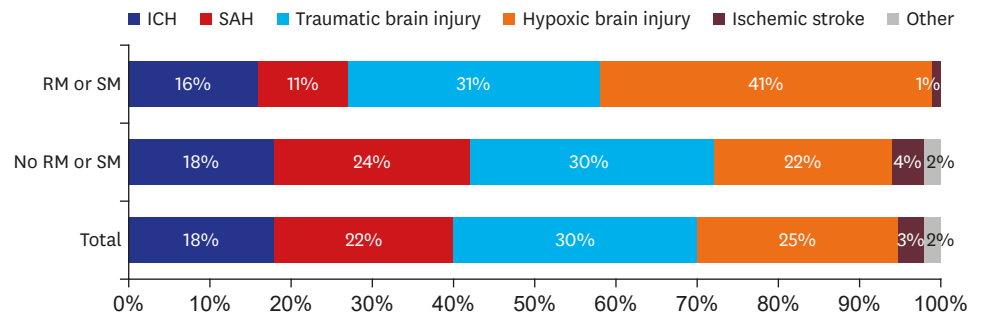
Of the 436 brain dead patients, 74 (17.0%) exhibited reflex or spontaneous movements. Of these, 45 (60.8%) exhibited reflex movements only, 18 (24.3%) exhibited spontaneous movements only, and 11 (14.9%) exhibited both. Of the same 74 patients, 53 (71.6%) were analyzed by video recordings and 21 (28.4%) did not have video recordings and were analyzed based on physicians' medical records. In addition, 52 (70.3%) patients exhibited one

Table 1. Demographics and clinical characteristics of the 436 patients with impending brain death

Characteristics	Value
Age, yr	48.8 ± 13.0
Gender, men	311 (71.3)
Height, cm	167.3 ± 9.4
Brain death causes	
ICH	78 (17.9)
SAH	95 (21.8)
Traumatic brain injury	132 (30.3)
Hypoxic brain injury	110 (25.2)
Ischemic stroke (cerebral infarction)	14 (3.2)
Other	7 (1.6)
Movements, all	
Only reflex	45 (10.3)
Only spontaneous	18 (4.1)
Both	11 (2.5)
SBP, mmHg	117.8 ± 19.6
DBP, mmHg	70.5 ± 14.1
HR, beats/min	92.3 ± 25.8
BT, °C	37.3 ± 0.7
pH	7.4 ± 0.1
Pressure of oxygen, mmHg	140.4 ± 77.4
Carbon dioxide pressure, mmHg	37.4 ± 9.0
Bicarbonate, mEq/L	22.3 ± 4.6
Fraction of inspired oxygen	55.9 ± 23.6

Data are presented as mean ± standard deviation or number (%).

ICH = intracerebral hemorrhage, SAH = subarachnoid hemorrhage, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, BT = body temperature.



	ICH (with or without IVH)	SAH (with or without IVH)	Traumatic brain injury	Hypoxic brain injury	Ischemic stroke	Other	Total
Total	78 (18%)	95 (22%)	132 (30%)	110 (25%)	14 (3%)	7 (2%)	436
No RM or SM	66 (18%)	87 (24%)	109 (30%)	80 (22%)	13 (4%)	7 (2%)	362
RM or SM	12 (16%)	8 (11%)	23 (31%)	30 (41%)	1 (1%)	0 (0%)	74

Fig. 2. Causes of brain death across all patients and with or without movement. Other etiologies include brain tumor, arteriovenous malformation, encephalopathy, osmotic myelinolysis. RM = reflex movement, SM = spontaneous movement, ICH = intracerebral hemorrhage, SAH = subarachnoid hemorrhage.

Table 2. Univariate analyses of reflex or spontaneous movements during the diagnosis of brain death

Characteristics	No SM or RM (n = 362)	SM or RM (n = 74)	P value
Age, yr	48.6 ± 13.1	49.7 ± 12.6	0.505
Gender, men	263 (72.7)	48 (64.9)	0.177
Height, cm	167.9 ± 7.9	166.1 ± 7.9	0.080
Cause of brain death			0.001
ICH	66 (18.2)	12 (16.2)	
SAH	87 (24.0)	8 (11.0)	
Traumatic brain injury	109 (30.1)	23 (31.1)	
Hypoxic brain injury	80 (22.1)	30 (40.5)	
Ischemic stroke	13 (3.6)	1 (1.4)	
Other	7 (1.9)	0 (0)	
SBP, mmHg	114.2 ± 17.7	135.1 ± 19.3	0.000
DBP, mmHg	68.4 ± 13.2	80.6 ± 14.4	0.000
HR, beats/min	93.6 ± 25.6	88.4 ± 24.7	0.109
BT, °C	36.6 ± 0.8	36.4 ± 0.6	0.220
pH	7.38 ± 0.09	7.40 ± 0.08	0.096
Pressure of oxygen	141.0 ± 76.4	137.5 ± 82.4	0.722
Pressure of carbon dioxide	37.5 ± 9.1	36.5 ± 8.2	0.385
Bicarbonate	22.0 ± 4.8	23.5 ± 4.3	0.013
Fraction of inspired oxygen	56.0 ± 23.4	55.5 ± 24.7	0.847

Data are presented as mean ± standard deviation or number (%).

RM = reflex movement, SM = spontaneous movement, ICH = intracerebral hemorrhage, SAH = subarachnoid hemorrhage, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, BT = body temperature.

Table 3. Logistic regression analyses of reflex or spontaneous movements during the diagnosis of brain death

Characteristics	OR	95% CI	P value
Age	1.022	0.997–1.047	0.085
Hypoxic brain damage	2.928	1.560–5.496	0.001
SBP	1.050	1.028–1.072	0.000
DBP	1.018	0.991–1.046	0.200
Bicarbonate	1.059	0.994–1.128	0.076

OR = odds ratio, CI = confidence interval, SBP = systolic blood pressure, DBP = diastolic blood pressure.

movement of the same pattern and 22 (29.7%) exhibited two or more different movement patterns; a total of 106 movements were observed in the 74 patients. The frequencies and characteristics of the movements are summarized in **Table 4**. The most common reflex

Table 4. Frequencies and descriptions of common reflex or spontaneous movements in patients during the process of determining brain death

Movement type	Description	Movements	Frequency, No. (%)
Flexor/extensor plantar response	Plantar flexion or extension, elicited by tactile or noxious plantar stimulation	RM	30 (28.3)
Isolated finger jerk	Brief movements of thumb or other fingers, spontaneous or elicited by tactile or noxious stimulation	RM or SM	11 (10.4)
Pronation extension arm reflex	Pronation and extension of the upper limb, elicited by noxious hand stimulation or spontaneous	RM or SM	10 (9.4)
Undulating toe flexion	Slow and repetitive flexion/extension movements of the toes, spontaneous or elicited by tactile or noxious foot stimulation	RM or SM	9 (8.5)
Triple flexion reflex	Flexion of the thigh, leg, and foot, elicited by noxious stimulation on the foot	RM	8 (7.5)
Head turning	Turning of head to a specific direction for several seconds, spontaneous or elicited by noxious stimulation	RM or SM	8 (7.5)
Myoclonus (spinal)	Contraction of a muscle or a group of muscles, particularly involving lower limbs or abdominal muscles	SM	7 (6.6)
Asymmetric opisthotonic posture	Back arching or twisting, spontaneous or elicited by noxious stimulation	RM or SM	6 (5.7)
Tonic neck reflex	Extensions of the arm and sometimes the leg on the side to which the head is forcibly turned, with flexion of the contralateral limbs	RM	5 (4.7)
Quadriceps contraction	Contraction of quadriceps, spontaneously or elicited by tactile or noxious stimulation on the lower limb	RM or SM	4 (3.8)
Respiratory-like movement	Adduction of shoulders and slow cough-like movements, spontaneous or elicited by stimulation	RM or SM	2 (1.9)
Lazarus' sign	Bilateral arm flexion, shoulder adduction, and hand raising to the chest/neck, seems to be grasping for endotracheal tube	RM or SM	2 (1.9)
Deep tendon reflex	Muscles immediately contract, elicited when a muscle tendon is tapped briskly	RM	2 (1.9)

RM = reflex movement, SM = spontaneous movement.

movement (n = 30, 28.3%) was the flexor/extensor plantar response. Of the 74 patients, 45 (60.8%) exhibited movements only in a limited area of the body with the leg being the most common (n = 26, 57.8%) whereas 29 (39.2%) exhibited these movements in multiple areas.

Comparisons of the demographic and clinical characteristics

Univariate analyses revealed that systolic blood pressure (SBP), diastolic blood pressure, and bicarbonate levels and cause of brain death were significantly higher in patients with reflex and spontaneous movements (Table 2). Subsequently, multivariate analyses revealed that hypoxic brain damage and a higher SBP were significantly associated with developing reflex and/or spontaneous movements (Table 3). There were no significant differences in terms of age, gender, heart rate, body temperature, blood pH, oxygen and carbon dioxide pressure levels, fraction of inspired oxygen or height.

DISCUSSION

Reflex and spontaneous movements associated with brain death have been evaluated in more than 130 studies of various designs ranging from animal studies to cohort studies.¹⁰ However, only a few have employed verified neurological examination and laboratory tests as a standard protocol when diagnosing brain death.³⁻⁶ The frequencies of reflex and spontaneous movements differ widely among studies and the most commonly reported movements vary as well. In Korea, a single prospective study of 26 adult patients at a single tertiary medical center in 2006 has been published.⁵ To the best of our knowledge, the present study included the largest sample of cases that has been used to investigate movements in brain dead patients.

We defined movements induced by stimulation as reflex movements, whereas self-appearing movements in the absence of stimulation were defined as spontaneous movements. These terms are clinically useful because all movements associated with brain death are divided into these two categories.⁹ Except for anecdotal reports, it was possible to confirm the

frequency results of two initial retrospective studies published in 1973 that investigated these movements.^{1,2} Ivan¹ reported that reflex or spontaneous movements were present in 39 of 54 brain dead patients (72.2%) and Jorgensen² observed these movements in 50 of 63 such patients (79.4%). Both studies found the frequency of such movements to be more than 70%, which is higher than the rates reported by recent studies. These two initial studies had some limitations in that the enrolled patients had not been diagnosed according to the brain death criteria of the American Academy of Neurology (AAN) and the protocols that elicited these movements were not standardized. Subsequently, Dösemeci et al.³ and Saposnik et al.⁴ reported that reflex or spontaneous movements were present in 18 of 134 (13.4%) and 47 of 107 brain dead patients (43.9%), respectively. These studies were prospective, met the AAN criteria for brain death, and performed standardized protocols to elicit movements. Most recently, Hosseini et al.⁶ reported reflex or spontaneous movements in 40 of 122 (32.8%) brain dead patients in a 1-year cross-sectional study conducted in a single organ procurement unit. The frequency of movements observed in these studies ranged from 13.4% to 43.9%, which is highly variable. In 2006, a total of 26 adult brain dead patients at a single Korean tertiary medical center were enrolled in a study.⁵ Five (19.2%) exhibited reflex or spontaneous body movements during the process of determining brain death. Our results are in line with their reported frequency.

The most frequent movements or common movements are mentioned as important outcomes in previous reports but differ from study to study.¹⁻⁶ In the present study, the most common movement was flexor/extensor plantar response (**Table 4**), which is consistent with the findings of Hosseini et al.⁶ Eleven (14.9%) patients exhibited both reflex and spontaneous movements and 25 (33.8%) patients exhibited more than two movement patterns in each patient. The greatest number of accompanied movement patterns are 4. Also, 29 (39.2%) patients exhibited these movements on multiple body areas. These results suggest that reflex and spontaneous movements can appear together in a single patient, and either a single or various movement patterns can occur on several body parts. Han et al.⁵ conducted the only previous study on this topic in Korea. They observed these movements in 19.2% of their patients, a similar rate to our findings (17.0%). However, the most common movement and distribution of brain death etiology differed between their study and ours. Han et al.⁵ reported that the most common movement was a pronation-extension reflex. In addition, there were no identified factors that were associated with these movements.

In 2005, Saposnik et al.⁴ reported that reflex and spontaneous movements were significantly more common when the cause of brain death was focal lesions and that brain dead patients had a high average BP. In addition, Hosseini et al.⁶ reported that the mean SBP was significantly higher in a group of brain dead patients that exhibited movement. We found that brain death was more frequent in patients with hypoxic brain damage than in those who sustained focal lesions, contrary to the findings of Saposnik et al.⁴ That study included 107 brain dead patients but only 9 had suffered from hypoxic brain injury and thus it was likely difficult to perform statistical analyses. In contrast to Saposnik et al.,⁴ we included 436 brain dead patients and 110 (25.2%) had hypoxic brain injury. Of these patients, 80 of 362 (22.0%) patients who did not exhibit movement and 30 of 74 (40.5%) who did exhibit movement had hypoxic brain injury. Although multivariate analyses revealed significant differences between these groups (OR, 2.928; 95% CI, 1.560–5.496; $P = 0.001$) (**Table 3**), it would be difficult to explain why patients with hypoxic brain injury were more likely to display movements than those with focal brain injuries. Likewise, Saposnik et al.⁴ could not provide an explanation regarding why there were more movements in brain dead patients with a focal injury.

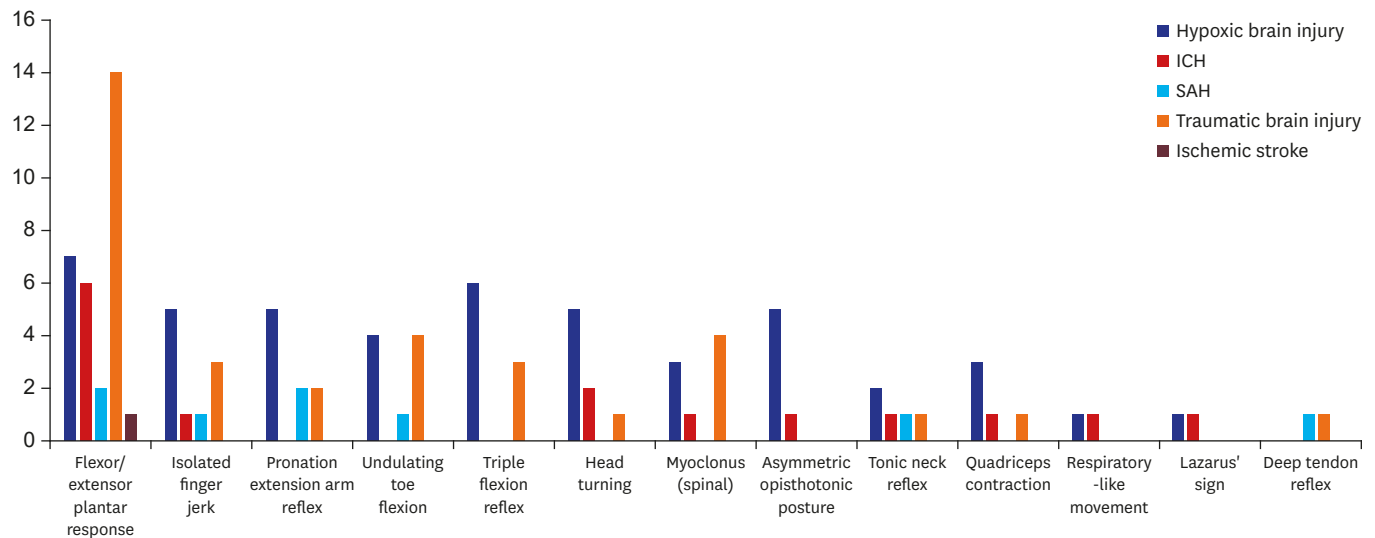


Fig. 3. Characteristics and frequencies of movements in patients classified by etiology of brain death. ICH = intracerebral hemorrhage, SAH = subarachnoid hemorrhage.

A previous study suggested that different types of myoclonus can be observed in the posthypoxic state.¹¹ We examined whether the significantly higher occurrence of these movements in hypoxic brain injury was associated with posthypoxic myoclonus. Of the 436 brain-dead patients, 110 had hypoxic brain injury. Of these, 30 had reflex or spontaneous movements. We examined the detailed reflex or spontaneous movements of the hypoxic brain injury patients. Myoclonus was observed only in three patients (two spinal myoclonus, one abdominal reflex). The most common movement found was flexor/extensor plantar response, not myoclonus, followed by a triple flexion reflex. The proportion of patients who had myoclonus was relatively small among hypoxic brain injury patients compared with other etiologies of brain death. In addition, myoclonus was observed in 8 of 74 patients with reflex or spontaneous movements and myoclonus appeared more often in patients with traumatic brain injury than in those with hypoxic brain injury (Fig. 3).

In conclusion, we analyzed reflex and spontaneous movements using a large sample of brain dead patients in Korea and found that 17.0% of patients exhibited these movements during the process of brain death diagnosis; the observed frequency is lower than that reported by previous studies. The occurrence of reflex and spontaneous movements in brain dead patients is not rare but previous studies of this phenomenon that employed relatively similar designs showed different results. In the present study, the flexor/extensor plantar response and isolated finger jerks were the most common movements and more movements were observed in patients with hypoxic brain injury and a higher SBP. If medical staff have sufficient knowledge of the frequency and patterns of these movements in patients with impending brain death, they may be better able to reduce delays in the diagnosis of brain death.

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