Original Research Article

Identification of separation phenomenon during brain death determination of potential organ donor and analysis of relative factors

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ABSTRACT

Background: With analyzing the incongruent phenomenon of electrical active and cerebral blood flow in brain death determination and screening the related factors, offer correct explanations and countermeasure to ensure the successful implementation of donation after brain death.
Methods: Relevant clinical data of potential brain death organ donors were prospectively collected between June 2018 and May 2019. The related parameters of neurological examination, laboratory examination and neuroimaging examination during the period of brain death determination were dynamically recorded. Separation phenomenon was used as grouping factors to screen the factors related to separation phenomena through univariate and multivariate analysis.
Results: According to the inclusion criteria, 127 patients were included in the study. Among 22 patients (17.3%) with incongruent phenomenon, 17 (77.3%) had electrical silence earlier than cerebral blood flow arrest, and 9 (22.7%) had cerebral blood flow arrest earlier than electrical silence. Univariate and multivariate analysis showed that age <14 years (OR=6.25, 95%CI 1.21-32.22, p=0.028), SBP≥140 mmHg (OR=7.43, 95%CI 1.62-33.99, p=0.010), primary brainstem injury (OR=15.89, 95%CI 3.04-82.93, p=0.006), spontaneous respiratory arrest time ≤72 hours (OR=11.96, 95%CI 1.59-89.78, p=0.009) and decompression craniotomy(unilateral or bilateral) (OR=16.28, 95%CI 2.25-117.73, p=0.001) were associated with separation phenomenon..
Conclusions: Separation phenomenon is a common during the confirmation test of brain death determination in China, and should be correctly recognized. To adopt corresponding measures according to risk factors is useful for successful implementation of donation after brain death.

Keywords: Brain death, Cerebral blood flow, Cerebral electrical activity, Confirmatory tests, Organ donation, Separation phenomenon

INTRODUCTION

According to China brain death determination standard, after reaching the clinical determination standard of brain death, potential brain death organ donation (DBD) donors must be conducted with confirmation examination.[1,2] As one of the confirmatory tests, the application of median nerve short latency evoked potential (SLSEP) in primary brain stem injury or children is limited, and it is hard to

be understand by patients' families and non-neurological healthy workers.

Therefore, in countries that have established the criteria for brain death, the vast majority of countries choose EEG and cerebral blood flow (CBF) assessment as the confirmatory test for brain death determination.[3,4] The phenomenon of absence of synchronous EEG silence and CBF arrest during the first confirmatory test of brain

death after meeting the criterion of clinical brain death, was called "separation phenomenon". Without correct understanding of "separation phenomenon", the determination of brain death may not be completed or delayed, which causing the failure of DBD implementation.

The incidence of "separation phenomenon" in another countries' reports is about 14%; it has been six years since the promulgation of China brain death criteria, but there are few relevant reports about separation phenomenon.[3] Our center has implemented brain death determination since 2015. Now, the "separation phenomenon" is analyzed and report as follows.

METHODS

Clinical data

From June 2018 to May 2019, the clinical data of potential DBD patients, admitted to the First Affiliated Hospital of Sun Yat-sen University, were collected prospectively. According to the China brain death determination standard and the principle of popularizing the concept of brain death, EEG and cerebral blood flow assessment were used as the first choice to confirm brain death.[1,2] According to the pre-designed research scale, with the bedside transcranial Doppler (TCD) and electroencephalogram (EEG) machine, the changes of EEG and CBF of patients were monitored synchronously and dynamically.

The relevant parameters of vital signs, neurological examination and laboratory examination were recorded synchronously until the brain death determination was completed. For patients with "separation phenomenon", further SLSEP examination or another EEG and CBF assessment were performed 24 hours later as intervention measures. This study was approved by the clinical research and experimental animal ethics committee of the First Affiliated Hospital of Sun Yat-sen University (Lun Shen [2019] 0220), and informed consent was obtained from the family members of the patients.

Inclusion criteria

The inclusion criteria of potential brain death patients were meeting the China clinical criteria of brain death; age more than 1 year; no other injury or lesions of body except brain.[1,2]

According to the inclusion criteria, 127 patients entered the study, including 103 males and 24 females, mean age is 33.2±15.2 years. The causes of death were traumatic brain injury in 71 cases (55.9%), spontaneous cerebral hemorrhage in 41 cases (32.3%), hypoxic-ischemic encephalopathy in 10 cases (7.9%), and intracranial tumor in 5 cases (3.9%).

Separation phenomenon

During the confirmatory test, the non-synchronous occurrence of EEG silence and cerebral blood flow arrest is called "separation phenomenon". There are two manifestations EEG silence is earlier than the CBF arrest; the CBF arrest is earlier than EEG silence.

The separation phenomenon is confirmed by two doctors who have the qualification of brain death determination.

Statistical methods

Based on the previous research of our center and relative research parameters, such as sex, age, time of spontaneous respiration arrest, blood pressure, operation method, neurological examination, neuroimaging index and serum Na+, were selected to screen the risk factors related to separation phenomenon through through univariate and multivariate analysis.[4-6] The statistical analysis was completed by SPSS software (version 22.0), $p<0.05$ was statistically significant.

RESULTS

In this study, 22 (17.3%) of 127 patients had separation phenomenon, 17 (77.2%) had EEG silence earlier than CBF arrest, and 5 (22.7%) had EEG silence earlier than CBF arrest. Univariate analysis showed that age ≤ 14 years, systolic blood pressure ≥140 mmHg, spontaneous respiration arrest time ≤72 h, anisocoria or dilated pupils, pupilary light reflex absent, primary brain stem injury, and decompressive osteotomy (unilateral / bilateral) were risk factors related to separation phenomenon (Table 1). Further multivariate analysis showed that age, systolic blood pressure, primary brain stem injury, spontaneous respiration arrest time ≤72 h and decompressive osteotomy (unilateral / bilateral) were independent risk factors for "separation phenomenon" (Table 2).

Table 1: The univariate analysis of separation phenomenon.

Factors	R	SD	Wald	OR （95%CI）	P value
Age ≤14 years	3.23	1.65	3.81	3.01 (0.97~1.05)	0.034
SBP≥140 mmHg	6.51	2.82	5.32	5.62(1.52~20.77)	0.001
SRAT≤72 h	6.17	2.66	5.34	5.31(1.41~19.97)	0.014
Anisocoria or dilated pupils	5.62	2.47	5.17	5.08(1.62~15.94)	0.005
Pupillary light reflex absent	4.27	2.31	3.41	4.79 (1.65~13.89)	0.004
Primary brain-stem injury	8.63	3.51	5.14	6.46 (2.00~20.89)	0.002
DC (unilateral or bilateral)	10.51	4.28	5.16	3.77 (1.24~11.49)	0.021

SBP= systolic blood pressure SRAT= spontaneous respiratory arrest time; DC= decompressive craniectomy.

Table 2: The multivariate analysis of separation phenomenon.

Factors	R	SD	Wald	OR（95%CI）	P value
Age ≤14 years	5.82	2.45	5.62	6.25 (1.21~32.22)	0.028
SBP ≥140 mmHg	9.13	4.25	4.61	7.43 (1.62~33.99)	0.010
Primary brain-stem injury	8.96	3.80	5.54	15.89 (3.04~82.93)	0.006
SRAT ≤72 h	6.67	2.91	5.24	11.96 (1.59~89.78)	0.009
DC (unilateral/bilateral)	11.42	4.88	5.47	16.28 (2.25~117.73)	0.001

SBP= systolic blood pressure, SRAT= spontaneous respiratory arrest time; DC= decompressive craniectomy.

DISCUSSION

The accurate implementation of brain death determination can ensure the successful implementation of DBD. According to China brain death determination standard, patients who meet the clinical standard of brain death can be identified as brain death only when at least two of the three confirmatory tests of EEG, CBF and SLSEP meet the standard.[1,2] For patients who was unable to evaluate five brain-stem reflexes, all the three confirmatory tests are required to meet the criteria of brain death.[1,2] On the premise of following the China brain death determination guidelines, the choice of confirmatory test should also combination with the patient's body state and the comprehensibility of examination results. SLSEP is hard to understand, while EEG and CBF are easy to be understood by patients' families and non-neurological healthy workers.[6,7] Therefore, the choice of EEG and CBF evaluation as the confirmatory test of brain death determination is conducive to the implementation of DBD.

The brain death confirmatory test is the objective result, which can be evaluated from morphology and function respectively and can increase the conviction of brain death determination; the combination of two or more confirmatory tests can improve the accuracy of brain death determination.[1,2,6,8] Yingying su et al, reported 131 patients who met the clinical standard of brain death; the results showed that the implementation rate of EEG was 98%, the sensitivity was 83% and the specificity was 97%; the implementation rate of TCD was 54%, the sensitivity was 73% and the specificity was 75%; the implementation rate of SLSEP was 49%, the sensitivity was 100% and the specificity was 78%; the sensitivity of EEG combined with TCD or SLSEP in brain death determination was 100%.[9] It can be seen that EEG and TCD can be selected as the confirmatory test method to ensure the accuracy of brain death determination and keep consistent with the international standard of brain death determination.[6,7] Therefore, the correct cognition and countermeasures to the "separation phenomenon" of EEG silence and CBF arrest can ensure the accuracy of brain death determination and the successful implementation of DBD.

Because of the difference of anatomical structure and function, the tolerance of each parts of brain tissue to ischemia and hypoxia is different, and this leads to different blood flow arrest and EEG silence in each parts,

which is the cause of "separation phenomenon."[10] Welschehold et al, conducted a single center retrospective study on 71 patients with brain death, which showed that 14% of the patients had an separation phenomenon of EEG silence and CBF arrest.[3] They took the strategy of waiting for 24-72 hours for patients with separation phenomenon, and finally diagnosed as brain death. In our study, 17.3% of patients (taking the strategy of waiting for 24-72 hours or increasing SLSEP test, and finally diagnosed as brain death) had the separation phenomenon, which was similar to the above-mentioned results.

Based on the concept of "time is brain", brain death is a gradual process along the time axis (since the injury factors are not effectively corrected, brain death is irreversible). In this process, the separation phenomenon of EEG silence and CBF arrest is affected by the cause of brain injury, the patient's body state and the stage of brain injury. Wijdicks et al, reported that age, cerebral perfusion pressure, type of brain injury, course of disease and operation techniques of confirmatory test were related to separation phenomenon.[11] Our study showed that systolic blood pressure ≥ 140 mmHg, age ≤14 years, primary brain stem injury, spontaneous respiratory arrest time ≤72 h and decompressive craniectomy (unilateral/bilateral) were independent factors of separation phenomenon. For the "pseudocerebral blood flow" caused by high systolic pressure and incomplete skull, further SLSEP examination is recommended to ensure the diagnosis of brain death and avoid further waiting leading to organ donation failure after brain death (the patients with brain death often suffer from cardiac arrest due to unstable circulation); for the primary brain stem injury and children (age ≤ 14 years), re-examination is recommended after 24-72 hours; because of brain stem conduction tract injury or hypoplasia SLSEP test is not recommended for patients; the patients with unstable circulation caused by waiting, can be treated with the "hormone package" (one of effective treatment of our center).[12-17] For patients with a short course of disease (such as spontaneous respiration arrest time ≤72 h), it is recommended to further carry out SLSEP test or wait for 24-72 h before carrying out the examination again.

In addition, this study also showed that 77.2% of the patients with separation phenomenon showed that the EEG silence was earlier than the CBF arrest, which showed that the CBF arrest in TCD had good consistency with EEG silence; meanwhile, TCD was not affected by

sedatives, the environment of ICU was interfered and easy to operate in bedside.[18,19] Therefore, for patients who meet the clinical criteria of brain death, TCD can be used as the confirmatory test of brain death in priority (for patients with skull defect, TCD is not used as the final confirmation test). Based on this, TCD can be regarded as a bridge to the diagnosis of brain death.[19]

The shortcomings of this study are single center study, there may be patient selection bias, exclusion of children, age less than 1 year. The results of our study need to be further verified by external research.

CONCLUSION

Separation of CBF arrest and EEG silence is common in the process of brain death confirmation test. To enhance the understanding of the separation phenomenon and take countermeasures against the relevant factors can ensure the accurate and successful implementation of brain death determination.

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