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ORIGINAL COMMUNICATION

The observation period after clinical brain death diagnosis according to ancillary tests: differences between supratentorial and infratentorial brain injury

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Abstract

Objective To determine the optimal observation period (OBP) in adults with a clinical diagnosis of brain death (BD) using electroencephalography (EEG) or computerized tomography angiography (CTA).

Methods We conducted a retrospective observational analysis of adult patients with a diagnosis of BD from January 2000 to February 2017. The optimal OBP was defined as the minimum time interval from the first complete clinical neurological examination (CNE) that ensures that neither a second CNE nor any ancillary test (AT) performed after this period would fail to confirm BD.

Results The study sample included 447 patients. In the supratentorial group, the first AT confirmed BD in 389 cases (98%), but in 8 (2%) cases the complementary test was incongruent. In this group, 8 of 245 patients in whom the first AT was carried out within the first 2 h after a complete CNE had a non-confirmatory test of BD versus none of 152 in whom the first AT was delayed more than 2 h (3.0% vs 0.0%; $p = 0.026$). In the infratentorial group, we found a higher probability of obtaining a first non-confirmatory AT of BD (34% vs 2%; $p = 0.0001$) and an OBP greater than 32.5 h was necessary to confirm a BD diagnosis.

Conclusions We found important differences in the confirmation of BD diagnosis between primary supratentorial and infratentorial lesion, and identified an optimal OBP of 2 h in patients with supratentorial lesions. By contrast, in primary posterior fossa/infratentorial lesions, the determination of an optimal OPB remains less accurate and hence more challenging.

Keywords Brain death · Observation period · Clinical examination · Ancillary test · Computerized tomography angiography · Electroencephalography

Introduction

Catastrophic brain injury can lead to a determination of death by neurological criteria or brain death (BD), defined as the irreversible and complete loss of brain function [1–3].

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Although there is agreement that the cornerstone of the BD diagnosis is the clinical neurological examination (CNE), many controversies persist and a global international consensus is needed to standardize clinical practices [4–9].

In some European countries such as Spain, the diagnosis of death using neurological criteria is based on a "whole BD" concept, which requires that all clinical functions of the entire brain, including those subserved by the cerebral hemispheres, diencephalon and brain-stem, have ceased [5, 6, 10–12]. Under this policy, an ancillary test (AT) is mandatory so as to examine both cerebral hemispheres in cases of primary infratentorial lesions [10, 11]. In contrast, some other countries, including the UK, Canada and India, support the concept of "brainstem death", and a complete CNE is enough to declare BD, regardless of the localization of the brain injury [12].

There is controversy regarding the recommended number of CNEs and minimum observation period (OBP) between examinations [7, 13]. It has been noted that no patients have ever recovered after a first complete BD CNE. Hence, many authors advocate omitting a second CNE, thus avoiding loss of potential organ donors [14–16]. This idea has gained ground in US, and the updated guideline of the American Academy of Neurology (AAN) is similar to the UK BD criteria since they do not recommend performing an AT if the clinical BD criteria are fulfilled [14]. However, Greer et al. [17] reported that most hospitals in US (65.9%) required two or more separate CNEs to declare BD and 20.9% carried out more than two. Most often, the minimum OBP between CNE was established to be at least 6 h in 71.1% of these hospitals. In Europe, Citerio et al. [5] examined the variability in BD determination in 28 countries and reported that 82% of them required more than one CNE to confirm BD, with a median for a minimum OBP of 3 [0–12] hours. In Spain, the recommended OBP between the first and second CNE is at least 6 h in supratentorial brain injury, or 24 h in hypoxic–ischemic encephalopathy [11].

The word "irreversible" inherently implies an OBP long enough to assure that brain functions will not return. The OBPs are arbitrary and, up to now, there is insufficient evidence to determine which is the minimally acceptable waiting time [14]. Of note, we recently reported that the incidence of electrocerebral activity on electroencephalography (EEG) despite clinical findings consistent with BD was 3.5% [18]. Thus, we have defined as the optimal OBP, the minimum time elapsed from the first complete CNE that would ensure that neither a second CNE nor any AT performed after this period would fail to confirm BD.

There is international consensus that an AT may be useful (or even mandatory in some countries) for declaring BD when there are confounding factors that could interfere with the CNE, for example, by the inability to complete the apnea test or when some reflexes of the CNE cannot be performed due to anatomic limitations or severe injuries [2, 4, 8, 12, 14]. Operationally, in these cases, the AT is equivalent to a second CNE. In addition, the Spanish legislation establishes that performing an AT after the first confirmatory CNE is sufficient to certify BD. Therefore, the period between the CNE and the AT may represent a valid OBP.

The aim of the present study was to determine the optimal OBP in adults with a complete clinical diagnosis of BD using EEG or computerized tomography angiography (CTA). We think that obtaining evidence-based data for BD diagnosis will improve and help standardize international guidelines.

Methods

Study design

We conducted a retrospective observational analysis of all the patients older than 14 years, admitted to our Neurointensive Care Unit (NICU) at "Marqués de Valdecilla" University Hospital, from January 2000 to February 2017 with a diagnosis of BD following the Spanish law [10, 11]. Our centre is a teaching hospital which provides care to near 590,000 inhabitants, and we have an official organ transplant program since 1984.

Inclusion criteria were for those patients with brain injury of known cause, without confounding factors and fulfilled prerequisites, in whom the determination of BD was carried out through the combination of a complete CNE, including apnea test and a confirmatory AT that corroborated the clinical diagnosis. We excluded patients if the cause of coma was in doubt, if there were confounding factors (such as hypothermia or sedative drugs), if the CNE was incomplete or the apnea test could not be performed. In addition, those patients in whom BD was established by two CNEs or who had had hypoxic–ischemic encephalopathy were excluded.

Because of the historical controversy regarding BD being one of whole BD versus brainstem death [19], we divided patients according to the anatomical localization of brain injury into two groups: supratentorial (SG) or infratentorial (IG). Patients with subarachnoid hemorrhage were included into the SG. All details of these data have been previously published as a Doctoral Thesis [20].

Determination of death by neurological criteria or brain death

Following Spanish law [10, 11], a systematic and rigorous CNE was carried out in all cases by a senior intensivist and certified by three physicians, one of them a neurosurgeon. According to our hospital protocol, we used two types of ATs to certify BD: EEG as a brain function test and CTA to evaluate cerebral blood flow (CBF). When the first AT did not confirm BD, another AT was performed. The prerequisites for clinical testing, conditions of CNE, regulation of OBP and ATs can be found in the supplementary material [18, 21, 22].

Data collection and analysis

Baseline demographic and clinical data as well as AT results were gathered from clinical charts according to a standardized protocol. We calculated the AT interval (ATI) as the time in hours between the date and the time of the complete CNE and the onset of the first AT (ATI-1) or subsequent testing (ATI-2, ATI-3, etc.). The brain death interval (BDI) was defined as the time in hours from the complete CNE to the certification of death. A summary of all collected information and details of the statistical analysis can be found as supplementary material. The study was approved by the local Ethics Committee.

Results

A total of 8226 patients were admitted to our NICU during the study period. A legal diagnosis of BD was obtained in 523 (6.3%) subjects. The cause and number of excluded patients were: incomplete CNE of BD due to failure to be able to complete the apnea test, 42 (8%); hypoxic–ischemic encephalopathy, 14 (2.7%); and diagnosis of BD exclusively by clinical criteria without AT, 20 (3.8%) (Fig. 1). In all 20 patients, the second CNE (including apnea test) was always confirmatory of BD and the median time of BDI was 6 [6–7.6] (mean 8.1 ± 4.0) hours.

The study sample thus included 447 (85.5%) patients with a complete CNE and at least one AT confirmatory of BD. Of these patients, 397 (88.8%) had a predominately supratentorial brain damage and 50 (11.2%) had primarily infratentorial lesions (Fig. 1). Overall, the median time of BDI was 2 [1–5] (mean 5.1 ± 7.7) hours. All demographic and clinical features of the study sample are summarized in Table 1.

In the SG, although an exclusively clinical diagnosis of BD could have been done by a second CNE after a minimum OBP of 6 h, an AT was performed following the recommendations of Spanish law to shorten the OBP. Of 397 patients, the first AT confirmed BD in 389 (98%), but in 8 (2%) the complementary test was not confirmatory. The ATI-1 in patients with confirmation of BD was 1.7 [1–3.5] (mean 3.5 ± 4.6) hours versus 0.6 [0.4–1.3] (mean 0.9 ± 0.5) when AT was non-confirmatory ($p = 0.004$).

The first AT was an EEG in 354 (89.2%) patients of the SG (Fig. 1). Of them, 350 (98.9%) showed electrocerebral inactivity. In two cases, the evaluation by a second electroencephalographer was required. In both cases, electrocerebral inactivity was confirmed. The median time of ATI-1 was 1.6 [1–3.5] hours (mean 3.6 ± 4.7 h). Only in 4 (1.1%) patients, the EEG showed persistence of electrocerebral activity. In these four cases, the ATI-1 was 1 h or less with a median of 0.5 [0.4–0.8] hours (mean 0.6 ± 0.2 h), lower than in cases with isoelectric EEG ($p = 0.007$). A second EEG was repeated between 16.5 and 23.2 h from CNE, showing electrocerebral inactivity in all cases. EEG patterns and clinical characteristics of these 4 patients can be found in Table 2.

In 43 (10.8%) of 397 cases with supratentorial lesions, CTA was the first AT (Fig. 1). Using the old CTA criteria (absence or persistence of intracranial contrast), 29 (67.4%) patients had absence of CBF and intracranial contrast was observed in 14 (32.6%). However, when we used the 4-vessel CTA criteria for BD confirmation [22], 39 (90.7%) patients had absence of CBF with a median of ATI-1 of 2 [1.2–4] hours (mean 3 ± 3 h). Only 4 (9.3%) subjects had evidence of contrast in any of the vessels evaluated. In these 4 patients, the ATI-1 was 2 h or less with a median of 1.1 [0.5–1.8] hours (mean 1.2 ± 0.7 h), lower than when CBF arrest was observed, but without statistical significance ($p = 0.1$). In all cases, EEG was selected as the second AT and showed electrocerebral inactivity between 9 and 25.5 h after the complete CNE (Table 2).

To select the cutoff point for the ATI, we perform an ROC curve analysis in the SG. The ATI of 2 h showed the best fit (sensitivity 42% and specificity 100%). In this group, 8 of 245 patients in whom the first AT was carried out during the first 2 h after a complete CNE, had a non-confirmatory test of BD versus none of 152 in whom the first AT was delayed for more than 2 h (3.0% vs 0.0%; $p = 0.026$). All results of 405 ATs in the SG related to the ATI are shown in Fig. 2.

On the other hand, the IG included 50 (11.2%) patients. In these cases, an AT was mandatory following Spanish legislation. Converse to the findings with primary supratentorial damage, we found a higher probability of obtaining a non-confirmatory AT of BD (34% vs 2%; $p = 0.0001$). Of note, there was no difference in the median value for ATI-1 between IG and SG (1.6 [1–3.5] h vs 2 [1–3.4] h; $p = 0.45$).

In primary posterior fossa lesions, EEG was selected as the first AT in 41 (82%) patients and CTA in 9 (18%). Of them, 11 (26.8%) of 41 EEGs and 6 (66.7%) of 9 CTA using 4-vessel criteria (7 when using old CTA criteria) were not confirmatory. The median ATI-1 between confirmatory and non-confirmatory first ATs was 1.7 [1–3] h. vs 3 [1.5–4.5] h. ($p = 0.15$). Second ATs were 16 EEGs and 1 CTA with a median ATI-2 of 24.1 [20.6–29.1] (mean 26.6 ± 10.1) hours. The unique CTA and 14 of 16 (87.5%) EEGs corroborated BD. In two patients, the second EEG showed persistence of electrocerebral activity for 22.5 and 32.5 h. The EEGs traces included a low diffuse voltage pattern and alpha-theta coma. A third EEG was necessary in these two patients for

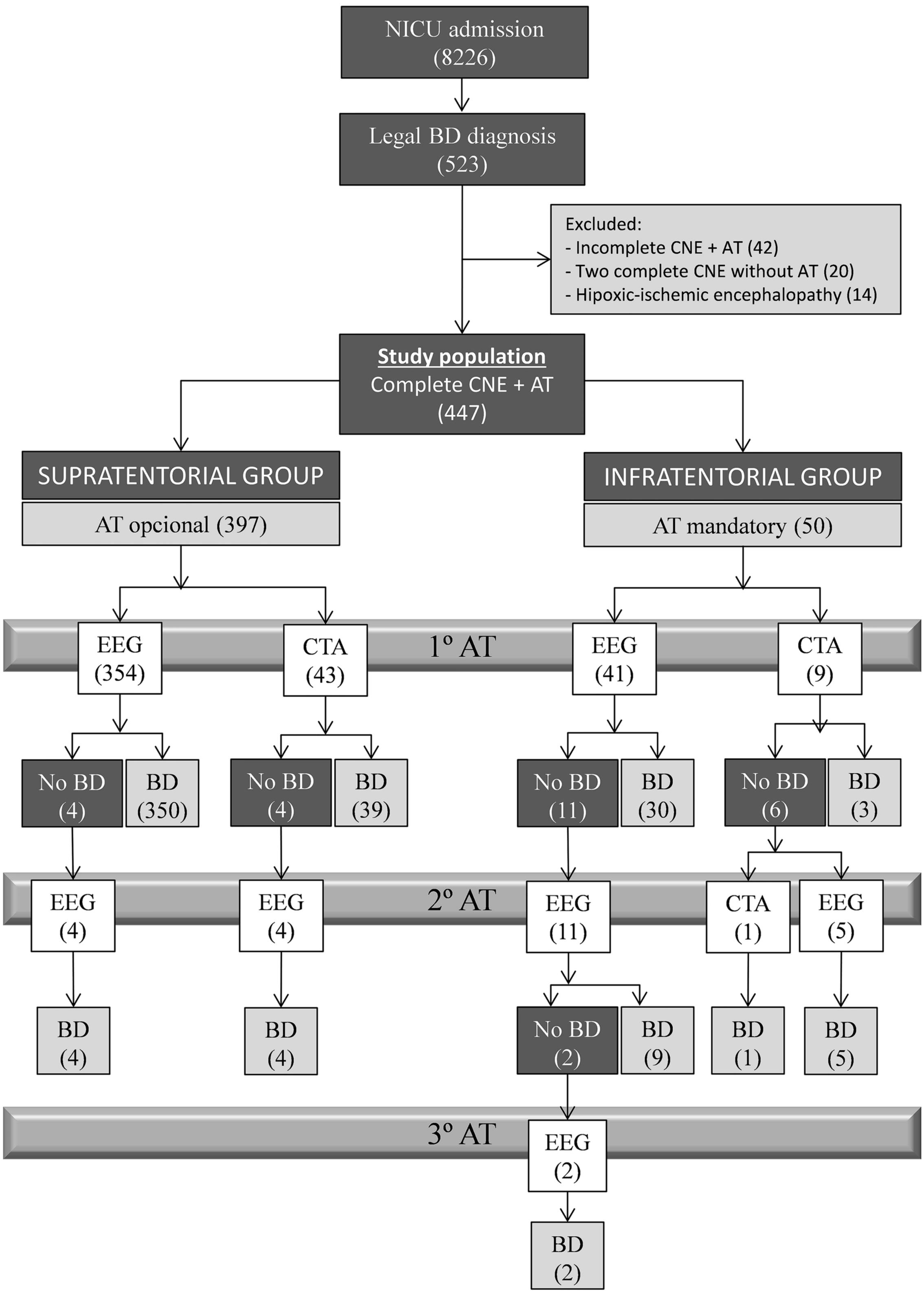

Fig. 1 Flowchart of study population. A number of patients are expressed in parentheses. *AT* ancillary test, *BD* brain death, *CNE* clinical neurologic examination, *CTA* computerized tomography angiography, *EEG* electroencephalogram, *NICU* neurointensive care unit

Table 1 Baseline characteristics of the study subjects by location of the primary brain injury

Variable	Supratentorial $N=397$	Infratentorial $N=50$	p
Sex, men	223 (56.2)	32 (64.0)	0.3
Age, mean ± SD	57.5 ± 16.8	61.4 ± 13.5	0.1
Cause of death			
Stroke	275 (69.3)	50 (100.0)	<0.0001
Cranial trauma	111 (28.0)	0 (0.0)	<0.0001
Other	11 (2.7)	0 (0.0)	0.6
Surgical procedure, yes	49 (12.3)	6 (12.0)	0.9
Decompressive craniectomy, yes	9 (2.3)	1 (2.0)	0.9
First ancillary test: EEG	354 (89.2)	41 (82.0)	0.1
Non-confirmatory of BD	4 (1.1)	11 (26.8)	<0.0001
First ancillary test: CTA	43 (10.8)	9 (18.0)	0.1
Non-confirmatory of BD	4 (9.3)	6 (66.7)	<0.0001
ATI-1 (h), mean ± SD, median [IQR]	3.5 ± 4.6 1.6 [1.0–3.5]	3.3 ± 3.8 2.0 [1.0–3.3]	0.4
BDI (h), mean ± SD, median [IQR]	4.2 ± 5.5 1.7 [1.0–4.0]	12.5 ± 15.1 3.2 [1.1–22.9]	0.01
Donation, yes	291 (73.3)	33 (66.0)	0.3
Family refusal, yes[a]	42 (12.6)	7 (17.5)	0.4

Percentages are expressed in parentheses

ATI ancillary test interval, *BD* brain death, *BDI* brain death interval, *CTA* computed tomography angiography, *EEG* electroencephalogram, *SD* standard deviation, *IQR* interquartile range

[a]Over total interviews ($n=373$)

confirming the electrocerebral inactivity (Fig. 1). The ATI-3 was 47.5 and 57 h (Table 2).

In patients with primary infratentorial damage, the median BDI was 3.2 [1.1–22.9] hours longer than 1.7 [1.0–4.0] hours in the SG ($p=0.012$). Results of 69 ATs performed in the 50 patients included in the IG are shown in Fig. 3.

Multivariable analysis showed that primary infratentorial damage (OR 24.2; 95% CI 8.7–66.8; $p<0.0001$) and an age younger than 50 years (OR 3; 95% CI 1–8.3; $p=0.04$) were associated with a higher probability of a first non-confirmatory AT. When the binary logistic model was exclusively applied to the SG, a shorter ATI-1 was the only variable associated with a non-confirmatory AT (OR 0.29; 95% CI 0.1–0.9; $p=0.04$).

Discussion

To the best of our knowledge, this is the first study focused on determining the optimal OBP after a complete CNE of BD, using EEG or CTA. We employed the same methodology to declare the BD as that used in Spain when a CNE cannot be completed. In these cases, the international consensus recommends an AT after the clinical assessment. In other European countries (e.g., Germany), the EEG would not be used (since lower brainstem function is not assessable on EEG), and only a test showing the cerebral circulatory arrest is allowed in such situations. If these investigations demonstrate residual cerebral electrical activity or CBF, a repetition of the test will be required to declare BD [4, 14, 23]. Here, we used an AT (EEG or CTA) as equivalent to a second CNE. Our results can be useful in standardizing approaches for the determination of BD.

In patients with supratentorial damage and a first complete clinical diagnosis of BD (including atropine and apnea test), 98% of the first ATs corroborated clinical assessment. All EEGs performed later than 1 h, and all CTAs later than 2 h, supported the diagnosis of BD. Moreover, there were no cases with a "reversible" clinical BD syndrome, when the BD was certified through a second CNE without AT. We considered non-confirmatory ATs of BD as true positives, and a second test was necessary to declare BD. Based on our findings, in patients with supratentorial lesions that meet all clinical criteria of BD, we propose an interval of at least 2 h as the optimal OBP for ensuring the permanent cessation of neurological functions.

In the SG, multivariable analyses showed that a shorter ATI was associated statistically with non-confirmatory AT (OR 0.29; 95% CI 0.1–0.9; $p=0.04$). This association between the ATI and the result of ATs has been previously reported in several blood flow investigations [24–26]. Of note, the study of Kerhuel et al. [26] found a much longer time period between the determination of the clinical BD

Table 2 Characteristics of patients with a first ancillary test non-confirmatory of brain death

N	Sex/age	Cause of admission	Type AT-1	Result AT-1 (EEG pattern/ CTA 4-pts score)	ATI-1 (h)	Type AT-2	Result AT-2 (EEG pattern/ CTA 4-pts score)	ATI-2 (h)	Type AT-3	Result AT-3 (EEG pattern/ CTA 4-pts score)	ATI-3 (h)	Neuroimaging
Supratentorial												
1	M/20	Stroke	EEG	Alpha-theta coma	0.5	EEG	ECI	23.2	–	–	–	Right frontal hematoma with massive tetraventricular hemorraghe
2	F/65	Stroke	EEG	Diffuse low voltage	0.5	EEG	ECI	16.5	–	–	–	SAH
3	M/59	Stroke	EEG	Alpha coma	0.5	EEG	ECI	20.0	–	–	–	SAH
4	F/35	TCE	EEG	Diffuse low voltage	1.0	EEG	ECI	20.5	–	–	–	Cerebral swelling, SAH
5	M/58	Stroke	CTA	2	0.5	EEG	ECI	13.9	–	–	–	Left hemispheric hematoma
6	F/44	Stroke	CTA	2	0.8	EEG	ECI	8.9	–	–	–	Left frontal hematoma
7	F/60	Stroke	CTA	0	1.5	EEG	ECI	10.7	–	–	–	SAH
8	M/63	Meningitis	CTA	0	2.0	EEG	ECI	25.5	–	–	–	Massive cerebral swelling
Infratentorial												
1	M/75	Stroke	EEG	Alpha-theta coma	0.6	EEG	ECI	25.6	–	–	–	Bihemisferic cerebellar hematoma
2	M/55	Stroke	EEG	Alpha-theta coma	0.7	EEG	ECI	25.2	–	–	–	Left cerebellar hematoma
3	M/51	Stroke	EEG	Diffuse low voltage	1.2	EEG	ECI	23.2	–	–	–	Basilar thrombosis
4	M/69	Stroke	EEG	Alpha coma	2.0	EEG	ECI	22.5	–	–	–	Left cerebellar hematoma
5	M/65	Stroke	EEG	Alpha coma	2.7	EEG	ECI	49.2	–	–	–	Basilar thrombosis
6	M/55	Stroke	EEG	Diffuse low voltage	3.0	EEG	Diffuse low voltage	22.5	EEG	ECI	47.5	Bihemispheric cerebellar infarct
7	M/44	Stroke	EEG	Alpha-theta coma	3.1	EEG	ECI	25.7	–	–	–	Basilar thrombosis
8	F/25	Stroke	EEG	Alpha coma	3.3	EEG	ECI	25.7	–	–	–	Cerebellar hematoma
9	F/69	Stroke	EEG	Alpha-theta coma	3.5	EEG	ECI	50.5	–	–	–	Right cerebellar hematoma

Table 2 (continued)

N	Sex/age	Cause of admission	Type AT-1	Result AT-1 (EEG pattern/ CTA 4-pts score)	ATI-1 (h)	Type AT-2	Result AT-2 (EEG pattern/ CTA 4-pts score)	ATI-2 (h)	Type AT-3	Result AT-3 (EEG pattern/ CTA 4-pts score)	ATI-3 (h)	Neuroimaging
10	F/79	Stroke	EEG	Alpha-theta coma	9.0	EEG	Alpha-theta coma	32.5	EEG	ECI	57.0	Basilar thrombosis
11	M/38	Stroke	EEG	Burst-suppression	10.7	EEG	ECI	14.2	–	–	–	Brainstem hematoma
12	M/49	Stroke	CTA	0	0.5	EEG	ECI	16.5	–	–	–	Right cerebellar hematoma
13	F/60	Stroke	CTA	0	1.7	EEG	ECI	18.0	–	–	–	Left cerebellar hematoma
14	F/66	Stroke	CTA	2	2.5	EEG	ECI	18.8	–	–	–	Vermix cerebellar hematoma
15	M/71	Stroke	CTA	0	3.6	EEG	ECI	24.1	–	–	–	Basilar thrombosis
16	M/41	Stroke	CTA	0	5.5	EEG	ECI	24.0	–	–	–	Right cerebellar hematoma
17	F/42	Stroke	CTA	0	9.9	CTA	4	34.9	–		–	Right cerebellar hematoma

AT ancillary test, *ATI* ancillary test interval, *BDI* brain death interval, *CTA* computed tomography angiography, *ECI* electrocerebral inactivity, *EEG* electroencephalogram, *F* female, *M* male, *SAH* subarachnoid hemorraghe

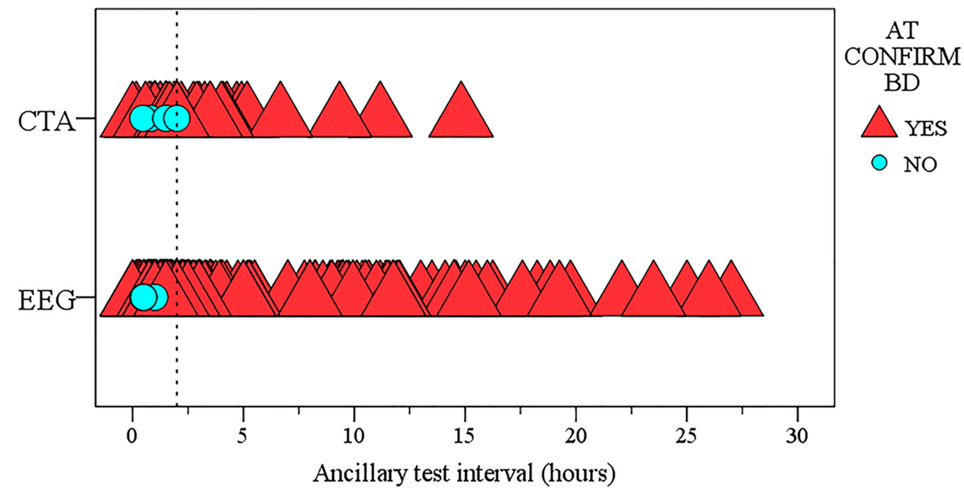

Fig. 2 Results of ancillary tests in the supratentorial group according to the ancillary test interval ($n=405$). *AT* ancillary test, *BD* brain death, *CTA* computed tomography angiography, *EEG* electroencephalogram

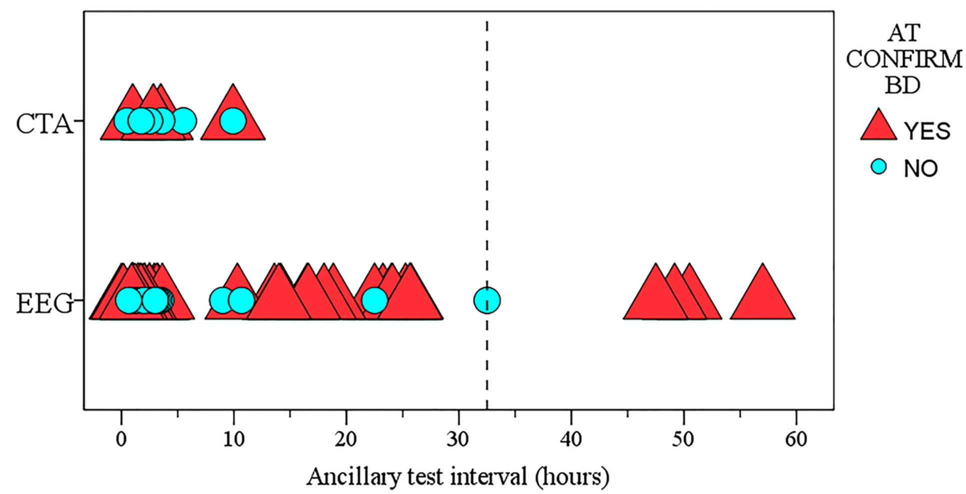

Fig. 3 Results of ancillary tests in the infratentorial group according to the ancillary test interval ($n=69$). *AT* ancillary test, *BD* brain death, *CTA* computed tomography angiography, *EEG* electroencephalogram

syndrome and the time point when nearly all CTAs were negative. It could be argued that a more rigorous screening for the onset of the clinical BD syndrome may lead to an earlier clinical BD determination and, as a consequence, to a longer time interval until confirmatory AT findings are obtained. However, the study by Kerhuel and colleagues [26] has important differences with respect to ours that might explain the greater persistence of CBF over time. They included patients with hypoxic–ischemic encephalopathy (21%), where CBF can persist for days despite the existence of a diagnosis of BD. Moreover, in more than half of the patients the examination of reflexes was not possible (9%) and the apnea test was not completed (44%). Therefore, our inclusion criteria were more demanding.

In the IG, a greater interval of 32.5 h as OBP was necessary for confirming BD diagnosis. In these patients, we found a 34% failure rate for ATs. Of note, one patient described by Varelas et al. [27] with primary posterior fossa lesion needed an interval of 6 days (144 h) to be declared BD. Thus, the optimal OPB for infratentorial lesions remains challenging.

Our study demonstrates that there are important differences in the confirmation of BD diagnosis using a first AT between primary supratentorial and infratentorial lesions. These results are not surprising because they may be due to the anatomical location and different pathophysiological mechanisms of primary lesions [19]. In a German study, Hoffmann and Masuhr [28] found that the first AT showed persistence of electrocerebral activity or perfusion, with a difference between primary supratentorial and infratentorial damage (2.9% vs 14.3%) similar to our study. Although multiple studies have also evaluated the global sensitivity of ATs for confirming clinical BD [13, 29–32], the specific data for each patient related to the primary location of the brain lesion, the failure to complete CNE and the interval from clinical BD to AT were not analyzed in detail.

Some case reports or short case series of non-confirmatory ATs of BD leading to delay in diagnosis have been published for primary infratentorial lesions [27, 33]. Of note, a comprehensive review by Walter et al. [34] has recently shown that the clinical brainstem death syndrome in patients with a primary infratentorial brain lesion cannot, with 100% certainty, be discriminated from total locked-in syndrome without ancillary testing.

Our study is the first to demonstrate that a primary infratentorial lesion was the most important variable associated with a non-confirmatory first AT despite complete CNE of BD (OR 24.2; 95% CI 8.7–66.8; $p < 0.0001$). This result supports the concept that in patients with posterior fossa injuries, an OBP cannot be accurately defined. Therefore, the need to perform an AT for declaring BD in this clinical situation appears to be sufficiently justified. An age younger than 50 years (OR 3; 95% CI 1–8.3; $p = 0.04$) was the other variable associated with a non-confirmatory first AT. This issue has not been previously reported, and a tentative explanation could be an increased resistance to ischemic damage of brain structures in younger patients [35].

The pathophysiological differences of BD depending on the site of the primary brain lesion could explain the discrepancies between clinical examination, electrical brain function and CBF. We found that CBF with almost residual contrast or stasis filling persisted for longer time than electrical brain activity in the SG, although less than 2 h in all the cases. Rostrocaudal herniation due to intracranial hypertension causes ensures that brainstem function is the last to disappear [2]. In contrast, in the IG, a non-confirmatory AT after a clinical diagnosis of BD was more frequent and delayed in days. In these cases, the first structure to be damaged is the brainstem and cortical function may be preserved for longer.

As in our study, a systematic review of CTA to BD diagnosis [36] concluded that the sensitivity of CTA changed according to interpretation criteria and was higher when the criterion for BD involved the lack of contrast of the internal cerebral veins (97–100%). We applied the 4-vessel CTA criteria instead of old CTA criteria (absence or persistence of intracranial CBF), showing a notable improvement in test sensitivity (80.8% vs 59.6%; $p < 0.0001$).

Prolonged BDI has been associated with economic costs and difficulties in the organ donation process [16]. Likewise, we have demonstrated that a BD diagnosis delay more than 6 h negatively affects the consent for organ donation [18]. Similar arguments were support by Varelas et al. [15] who found lower costs when a single BD examination was compared with a dual BD examination. However, OBPs were longer than 6 h, with a mean of BDI of 14.4 ± 12.9 h, three times higher that our mean of 5.1 ± 7.7 h.

Our study has some limitations. Firstly, it is based on a single hospital experience, and may not be applicable to other institutions with different populations. Second, it is a retrospective investigation, which may have introduced biases and weakened the results due to missing data in some of the variables. There was no a strict protocol used to determine the exact moment at which BD was clinically suspected, which was based on the presence of mydriasis, loss of the cough reflex detected by the nurses during the endotracheal suctioning and the drop to 0 of the bispectral index value when it was available. Therefore, some of these data could be lost in the retrospective review of the medical records.

Only two ATs (EEG and CTA) were employed for completing BD diagnosis and radionuclide scintigraphy, somatosensory and brainstem auditory evoked potentials and TCD were not included [37–39]. Moreover, the low number of cases and wide ATI range for non-confirmatory ATs could detract value to our results in the IG.

Conclusions

Our study demonstrates that there are important differences in the confirmation of BD diagnosis by EEG or CTA when comparing primary supratentorial and infratentorial lesions. Using an AT (EEG or CTA) as equivalent to a second CNE, we have identified an optimal OBP of 2 h in patients with supratentorial damage. By contrast, in primary posterior fossa lesions, a greater interval of up to 32.5 h is necessary to confirm BD. The optimal OPB for infratentorial lesions remains unclear.

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Compliance with ethical standards

Ethical standards The authors declare that this research has been approved by the appropriate ethics committee and has, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Spanish laws have been observed, too.

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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