



Brain death in children: is computed tomography angiography reliable as an ancillary test?

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Abstract

Background The diagnosis of brain death is primarily clinical. Sometimes ancillary tests are needed.

Objective This study compared sensitivity and interobserver agreement of the 10-, 7- and 4-point CT angiography scoring systems for the diagnosis of brain death in children.

Materials and methods CT angiography examinations of 50 pediatric patients with a clinical diagnosis of brain death were evaluated according to 10-, 7- and 4-point scoring systems. Images were evaluated by two radiologists who considered the vessel opacification first in the arterial phase (A_0-V_{50}) and then in the venous phase (A_0-V_{50}). We evaluated interobserver agreement for the assessment of vessel opacification and diagnosis of brain death. We compared the differences among brain death diagnoses between children with craniotomy–craniectomy defects, open fontanelles and preserved bone integrity. We subdivided children into two groups according to age: ≤ 2 years and > 2 years. We calculated sensitivities according to age groups.

Results Using the clinical exam as the reference standard, we found sensitivities for 10-, 7- and 4-point scoring systems to be 70%, 88% and 92% in the A_0-V_{50} method and 40%, 82% and 82% in the $A_{50}-V_{50}$ method, respectively. Percentage agreement between readers was 78% for the 7-point scale using the A_0-V_{50} method and more than 90% for other scoring systems for both the A_0-V_{50} method and the $A_{50}-V_{50}$ method. The sensitivity was much lower in children with open anterior fontanelles compared to the groups with preserved bone integrity and with a craniotomy–craniectomy defect.

Conclusion Just as in adult age groups, in children the 4-point scale appears to be more sensitive than the 10- and 7-point scales for CT angiography-based assessment of brain death. Because the scoring systems have similar sensitivities, they could be used as ancillary tests in pediatric cases.

Keywords Ancillary test · Brain death · Cerebral vessels · Children · Computed tomography angiography

Introduction

Brain death is defined as irreversible cessation of all brain functions, including those of the brainstem. The diagnosis is made clinically in accordance with the principles set out in the guideline, with the absence of brainstem reflexes and the presence of a positive apnea test in the comatose patient [1–3]. However, in some cases (e.g., severe fascial trauma and severe lung damage) these clinical tests are not performed. In these cases, ancillary

tests are needed [4]. In some European countries, ancillary tests are routine in addition to clinical diagnosis [3, 5, 6].

The term "ancillary test" is preferred to "confirmatory test" because these tests assist clinicians in making the clinical diagnosis of brain death. Ancillary studies can also be helpful for social reasons, allowing family members to better accept the diagnosis of brain death [7].

Ancillary tests include cerebral angiography, transcranial Doppler US, nuclear medicine perfusion, electroencephalography (EEG), CT angiography, CT perfusion imaging, magnetic resonance (MR) angiography and MR perfusion imaging [8, 9]. Among them, cerebral angiography is considered the gold standard [9]. Of these tests, CT angiography stands out for being easily accessible and fast and for providing anatomical information [1, 5, 10]. It is also a less operator-dependent examination than cerebral angiography. However, it has disadvantages such as radiation dose

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and contrast agent use. There can also be false positivity in hypotensive children and false negativity in children with craniectomy [6].

No consensus exists for a CT angiography imaging protocol or for reaching a diagnosis of brain death. Some authors have evaluated arteries in the arterial phase and veins in the venous phase [4, 11], while others have evaluated all vascular structures in the venous phase [2, 12–14]. Still other authors used evaluations in a single phase taken only at 40 s or 60 s [5, 8]. In addition to 10-point, 7-point and 4-point scoring systems, some authors have created different scoring systems by including the superior petrosal vein [3, 14, 15].

In the pediatric age group, the diagnosis of brain death has several characteristics. The diagnosis is based on the 1987 American Academy of Pediatrics guideline and its 2011 revision [7, 16]. This guideline states that brain death should not be diagnosed in newborns at fewer than 37 gestational weeks. In general, ancillary tests are not recommended in the diagnosis of brain death, but the guideline emphasizes that brain death diagnosis should be performed when clinical tests and apnea tests cannot be performed or completed [7, 16]. The guideline states that although the sensitivities of both EEG and cerebral blood flow tests are low in newborns between 37 gestational weeks and 30 days of age, the cerebral blood flow test is preferable, whereas between the ages of 30 days and 18 years, EEG and cerebral blood flow have equal sensitivity [7, 16]. The guideline emphasizes that transcranial Doppler US, CT angiography and MR angiography imaging modalities are not recommended because of insufficient studies in infants and children [7].

A literature survey yielded some studies on the use of CT angiography in the diagnosis of brain death; these studies mainly concern the adult age group. To the best of our knowledge, no studies have dealt with the pediatric age group alone. In the present study, we included only pediatric patients and evaluated the opacifications of vascular structures based on 10-, 7- and 4-point scoring systems for arterial and venous phases. We considered the clinical diagnosis as definitive and evaluated the sensitivity of these scoring systems and interobserver agreement for opacification of the vessels and brain death diagnosis. We compare our results with those of studies predominantly in adults, and we highlight the differences.

Materials and methods

This retrospective study was approved by the local ethics committee.

We retrospectively reviewed children between 1 month and 18 years of age who underwent a CT angiography examination between January 2015 and October 2021 and had a preliminary diagnosis of brain death. In total, we included 50 children younger than 18 years who had been clinically diagnosed as brain dead and had CT angiography as an ancillary test. All

children were clinically diagnosed with brain death before CT angiography. We excluded children for whom the venous phase could not be evaluated for technical reasons, those for whom evaluation of the opacification could not be performed because of severe pseudo-subarachnoid hemorrhage, and those for whom apnea tests were not conducted.

Image acquisition

All images were obtained with a 256-slice CT scanner (Somatom Definition Flash by Siemens, Erlangen, Germany; and iCT 256 by Philips Healthcare, Best, The Netherlands). From the C1–C2 level to the convexity was scanned three times with 1-mm section thickness. First, non-contrast images were obtained. After the pre-contrast examination, 2 mg/kg of intravenous (IV) contrast medium was administered. The second scan (arterial phase) was obtained when the ascending aorta opacification was over 150 Hounsfield units (HU) after contrast medium administration and the third scan (venous phase) was obtained 50 s after the second. Multiplanar reformatted images and maximum-intensity projections were also used in the evaluation of CT angiography.

Image interpretation

On non-contrast images, intra- and extra-axial hemorrhage, the presence of pseudo-subarachnoid hemorrhage, cranial bone integrity and the condition of the anterior fontanelle were evaluated and recorded. All CT angiography examinations were evaluated by two radiologists (E.A. and E.B., each with 7 years of CT angiography experience) who were blinded to each other's findings.

In the arterial phase, first we evaluated the superficial temporal arteries and decided the suitability of the examination. We evaluated and recorded opacifications of the middle cerebral artery M4 segments, anterior cerebral artery A3 segments, posterior cerebral artery P2 segments and basilar arteries. We also calculated the interobserver reliability for the opacification evaluations of vascular structures.

In the venous phase, we evaluated opacifications of middle cerebral artery M4 segments, anterior cerebral artery A3 segments, posterior cerebral artery P2 segments and basilar artery, as well as opacifications of the internal cerebral veins and great cerebral vein. We also calculated interobserver reliability for the evaluations of vascular structure opacifications.

Next, the two radiologists (E.A. and E.B.) evaluated brain death using the 10-, 7- and 4-point scoring systems. Results are presented in Table 1. They used two methods:

- 1) A_0-V_{50} : middle cerebral artery M4 segments, anterior cerebral artery A3 segments, posterior cerebral artery P2 segments and basilar artery evaluated in the arterial

Table 1 Summary of radiologic scores for determining brain death

Vessel	10-point scoring	7-point scoring	4-point scoring
Middle cerebral artery M4 (right and left)	2	2	2
Anterior cerebral artery A3 (right and left)	2	2	-
Posterior cerebral artery P2 (right and left)	2	-	-
Basilar artery	1	-	-
Internal cerebral vein (right and left)	2	2	2
Great cerebral vein	1	1	-
Sum of scores	10	7	4

One point is given for non-opacification of each vessel

phase as well as the internal cerebral veins and great cerebral vein evaluated in the venous phase; and

- 2) A_{50} - V_{50} : middle cerebral artery M4 segments, anterior cerebral artery A3 segments, posterior cerebral artery P2 segments, basilar artery, internal cerebral veins and great cerebral vein evaluated in the venous phase.

Full score means consistent with brain death and less than full score means not consistent with brain death. We examined interobserver reliability of brain death diagnoses made by each scoring system — 10-, 7- and 4-point scoring systems — using both A_0 - V_{50} and A_{50} - V_{50} methods. After these evaluations, both radiologists reached agreement on vascular structures' opacification and a final score for diagnosis of brain death according to the 10-, 7- and 4-point scoring systems using both A_0 - V_{50} and A_{50} - V_{50} methods.

We calculated the sensitivity of the scoring systems using consensus scores and evaluated the percentages of artery opacification in the arterial phase and the percentages of artery and vein opacifications in the venous phase. Then we compared the differences in the brain death diagnoses in children with impaired bone integrity or open fontanelle with brain death diagnoses in children with preserved bone integrity.

Moreover, to emphasize the difference in sensitivity of CT angiography in younger children, we divided the children into two groups according to age, ≤ 2 years and > 2 years. We calculated CT angiography sensitivities in the diagnosis of brain death for both age groups according to the 10-, 7- and 4-point scoring systems using both methods (A_0 - V_{50} and A_{50} - V_{50}). Further, we evaluated presence of cerebral edema and tonsillar herniation in contrast-enhanced and non-contrast-enhanced examinations.

Statistical analyses

To evaluate the interobserver reliability for the opacification evaluations of vascular structures, we used weighted kappa statistics, calculating kappa coefficients for each vessel. We

took the average of both sides for the double-sided vessels. Likewise, for each of the three scoring systems, we calculated kappa value with the percentage of reliability for the brain death diagnoses. Kappa values normally lie between 0 and 1, where 0 indicates an agreement purely by chance and 1 indicates perfect agreement. Calculated kappa values were interpreted as follows: < 0.20 , poor agreement; 0.21 – 0.40 , fair agreement; 0.41 – 0.60 , moderate agreement; 0.61 – 0.80 , good agreement; and 0.81 – 1.00 , very good agreement. Statistical analyses were performed using SPSS software (version 23.0; IBM, Armonk, NY).

Results

Fifty children (24 girls and 26 boys) who had been clinically diagnosed with brain death were included in the study. The median age was 61.5 months (range, 6–202 months). Among the causes of coma were trauma, terminal stage tumor, infection, intracranial hemorrhage and cardiopulmonary arrest of unknown etiology. The causes of coma are given in Table 2.

All 50 CT angiograms were technically adequate, with opacification of both superficial temporal arteries in the arterial phase indicating adequate intravenous bolus contrast injection, adequate cardiac output and proper exam timing (Fig. 1).

For the interobserver reliability of the scale for artery opacification in the arterial phase, the highest interobserver reliability was in the middle cerebral artery M4 segment at 97% ($k=0.72$) and the lowest was in the basilar artery at 92%

Table 2 Causes of coma in study patients ($n=50$)

Cause	n (%)
Terminal stage tumor	18 (36)
Trauma	14 (28)
Cardiopulmonary arrest of unknown etiology	12 (24)
Infection	4 (8)
Hemorrhage	2 (4)
Total	50 (100)

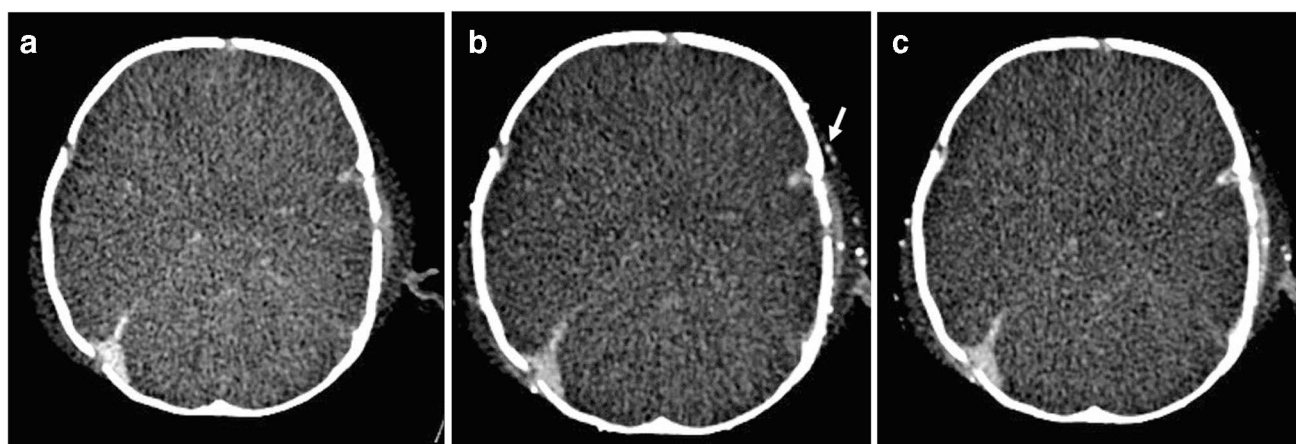


Fig. 1 CT angiography findings in a 6-month-old boy with brain death. **a** Axial pre-contrast CT image (WL:40, WW:80) shows sulcal effacement and loss of gray–white matter differentiation. **b** Axial post-contrast arterial-phase image (WL: 52, WW: 80) shows opacification of superficial temporal artery (*arrow*), which indicates adequate technique. **c** Axial post-contrast venous-phase image (WL: 58, WW: 118) shows absence of opacification of the middle cerebral arteries and branches. This boy was diagnosed with brain death both clinically and radiologically. *WL* window level, *WW* window width

($k=0.79$). In the venous phase, interobserver evaluation of the scale for vessel opacification showed highest reliability in the middle cerebral artery M4 segment at 99% ($k=0.95$) and lowest in the anterior cerebral artery A3 segment at 83% ($k=0.46$). Interobserver evaluations of vascular structures in the arterial and venous phases are presented in Table 3.

Regarding interobserver reliability among scoring systems, the interobserver reliability for the 7-point scoring system in the A_{50} – V_{50} method was moderate (78%, $k=0.42$). The interobserver reliabilities of the other scoring systems in both the A_0 – V_{50} method and the A_{50} – V_{50} method and opacification of the other vessels were more than 90% and had good or very good agreement levels. The interobserver compatibility of scoring systems and opacification of vessels in the arterial and venous phases are listed in Table 4.

Table 3 Interobserver agreement and kappa values for vessel opacification on CT angiography

	Arterial phase		Venous phase	
	k	Interobserver agreement, <i>n</i> (%)	k	Interobserver agreement, <i>n</i> (%)
Middle cerebral artery M4	0.72	97 (97)	0.95	99 (99)
Anterior cerebral artery A3	0.64	95 (95)	0.46	83 (83)
Posterior cerebral artery P2	0.78	93 (93)	0.78	90 (90)
Basilar artery	0.79	46 (92)	0.84	46 (92)
Internal cerebral vein	-	-	0.68	95 (95)
Great cerebral vein	-	-	0.54	47 (94)

adequate technique. **c** Axial post-contrast venous-phase image (WL: 58, WW: 118) shows absence of opacification of the middle cerebral arteries and branches. This boy was diagnosed with brain death both clinically and radiologically. *WL* window level, *WW* window width

Based on the consensus evaluation of vessel opacity, the lowest level of opacity scoring of arteries in the arterial phase was observed in the middle cerebral artery M4 segment, followed by the anterior cerebral artery A3 segment. The vessels with the least opacification in the venous phase were internal cerebral vein and great cerebral vein, while the middle cerebral artery M4 segment and anterior cerebral artery A3 segment were the arteries with the lowest opacification. The opacification numbers and percentages of vascular structures included in the scoring are described in Table 5.

We also compared the scoring systems and our findings regarding the number and percentages of children diagnosed with brain death (with full score) according to the 10-, 7- and 4-point scoring systems (Figs. 2 and 3) using the A_0 – V_{50} and A_{50} – V_{50} methods as listed in Table 6. Likewise, we compared the scoring systems in groups divided by age, calculating sensitivities for CT angiography in the diagnosis of brain death according to age ≤ 2 years or > 2 years using the 10-, 7- and 4-point scoring systems to reveal the CT angiography sensitivity in younger children, also using both methods (Table 7). When the clinical diagnosis was considered the standard reference, the sensitivities of the scoring systems created using the A_0 – V_{50} method were higher (Fig. 2).

Another factor we examined in this study was bone integrity. Bone integrity was impaired by craniotomy–craniectomy defects in 26 of the 50 children in the study and by an open anterior fontanelle in 8 children; bone integrity was maintained in 13. The other 3 children had both craniotomy–craniectomy defects and open anterior fontanelles. Tables 8, 9 and 10 show the number of children with brain death diagnosis based on the 10-, 7- and 4-point scoring systems evaluated in the A_0 – V_{50} and A_{50} – V_{50} methods and the sensitivities of the scoring systems with reference to the

Table 4 Interobserver agreement for CT angiography confirmation of brain death using 10-, 7- and 4-point scoring systems

Scoring system	Agreement for diagnosis of brain death, A ₀ -V ₅₀ method		Agreement for opacification of vessels in arterial phase		Agreement for diagnosis of brain death, A ₅₀ -V ₅₀ method		Agreement for opacification of vessels in venous phase	
	k	%	k	%	k	%	k	%
10-point	0.88	92	0.69	94	0.88	94	0.71	92
7-point	0.80	94	0.64	95	0.42	78	0.66	93
4-point	0.69	94	0.70	96	0.77	94	0.82	97

clinical diagnosis in children with preserved bone integrity, open anterior fontanelle and craniotomy–craniectomy defects.

Intracranial hemorrhage or pseudo-subarachnoid hemorrhage appearance were present in 38 children (Fig. 4). Diffuse cerebral edema and tonsillar herniation were observed in 48 children. In the two children without edema and tonsillar herniation, all vascular structures were opacified.

All vascular structures were opacified in three children (Fig. 5). In one of these children, the anterior fontanelle was open and no bone defect was found, in one child the anterior fontanelle was closed and associated with a bone defect and the third child had both bone defects and an open anterior fontanelle. Cerebral edema and tonsillar herniation were observed in the child who had both bone defects and an open anterior fontanelle, whereas the other two children did not have edema.

Discussion

First used in 1998 by Dupas et al. [11] for the diagnosis of brain death, CT angiography has been used as an ancillary method and been subject to much research since [2–5, 8, 10–15, 17–23]. Although there is still no consensus, 10-, 7- and 4-point scoring systems have been established, and their sensitivity has been calculated mostly in adult patients with clinically diagnosed brain death [4, 5]. The advantages of CT angiography over other ancillary tests have been evaluated [15, 17, 21, 23]. Most studies in the literature have mainly dealt with the adult age group, and no prior study, to the best of our knowledge, was conducted on the use of CT angiography in the diagnosis of brain death in pediatric patients.

The present study included pediatric patients, clinically diagnosed as brain dead. We ascertained the interobserver reliability for opacification of vascular structures and diagnosis of brain death according to 10-, 7- and 4-point scoring systems. Additionally, we investigated the sensitivities and differences of these scoring systems among children with skull defects, with open anterior fontanelle and without skull defects but with closed anterior fontanelle. Because CT angiography was not performed on any children whose clinical tests were not completed, we could not evaluate the specificity.

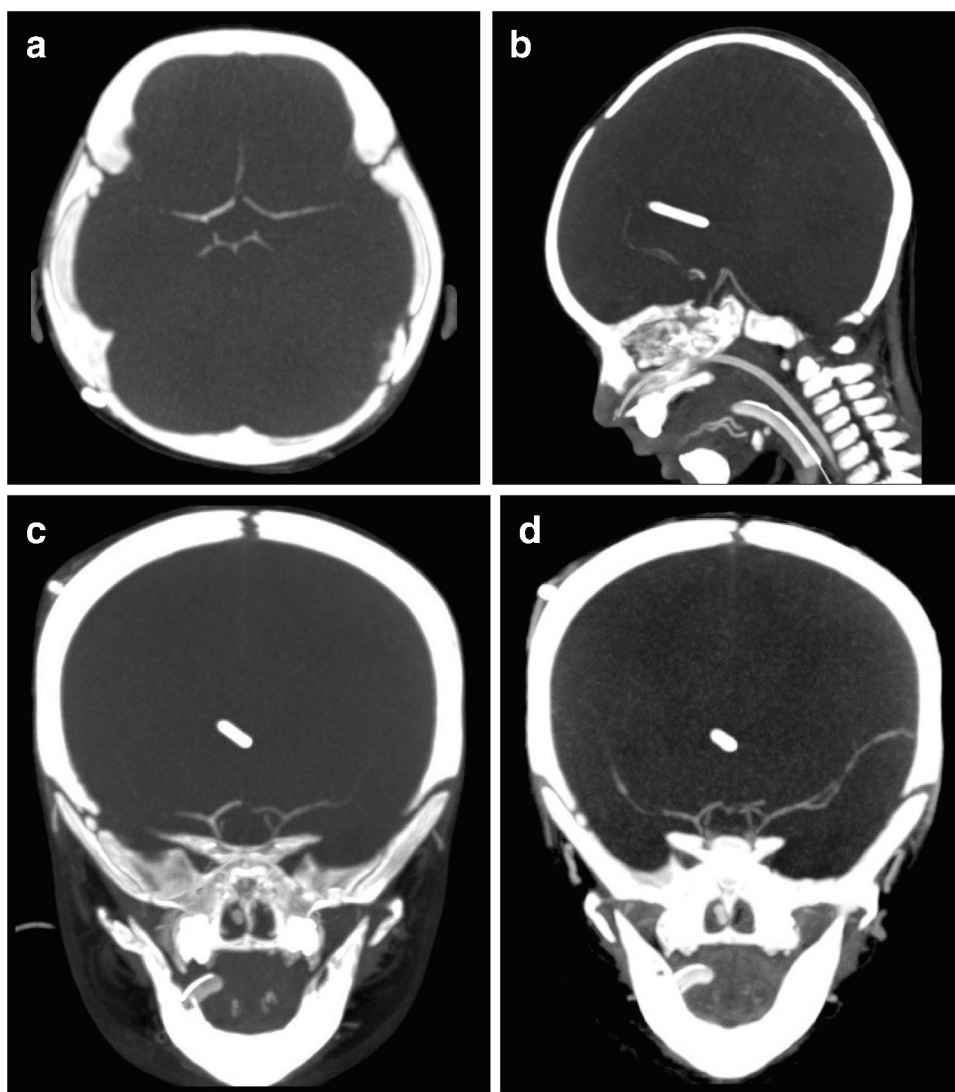
In our study, the interobserver agreement was good for all scoring systems in the A₀-V₅₀ method. In the A₅₀-V₅₀ method, the 10-point scoring had very good agreement, 4-point scoring had good agreement and 7-point scoring had moderate agreement. This might be a result of low agreement in the evaluation of anterior cerebral artery A3 segment in the venous phase. We think low agreement might be associated with the presence of pseudo-subarachnoid hemorrhage, which is more prominent in the venous phase [19].

In our study, the sensitivities of 10-, 7- and 4-point scoring systems were 70%, 88% and 92% for the A₀-V₅₀ method and 40%, 82% and 82% for the A₅₀-V₅₀ method, respectively. The sensitivity of the 4-point scoring system was similar to that of the 7-point system in the A₅₀-V₅₀ method, which was superior to the 7-point scoring in the A₀-V₅₀ method and to the 10-point scoring in both the A₀-V₅₀ and A₅₀-V₅₀ methods. Similarly, in prior studies, the sensitivity of the 4-point scoring system was superior to the scoring systems involving more vascular structures [4, 5]. Frampas et al. [10], Marchand et al. [3], Nunes et al. [19], Srairi et al. [14] and Şahin and Pekçevik [4] found the sensitivities of

Table 5 Number and percentage of opacified vessels on arterial and venous phase CT scans

Vessel	Arterial phase		Venous phase	
	Right	Left	Right	Left
Middle cerebral artery M4	2 (4%)	2 (4%)	4 (8%)	6 (12%)
Anterior cerebral artery A3	4 (8%)	3 (6%)	5 (10%)	5 (10%)
Posterior cerebral artery P2	11 (22%)	8 (16%)	19 (38%)	18 (36%)
Basilar artery	11 (22%) (single)		28 (56%) (single)	
Internal cerebral vein			4 (8%)	4 (8%)
Great cerebral vein			3 (6%) (single)	

Fig. 2 CT angiography findings in a 9-month-old girl. **a** Axial maximum-intensity projection reformat from post-contrast arterial-phase (WL: 296, WW: 723) image shows opacification of both posterior cerebral artery P2 segments. **b** Sagittal maximum-intensity projection reformat image from post-contrast arterial-phase (WL: 230, WW: 533) shows opacification of anterior cerebral artery A3 segments. **c** Coronal maximum-intensity projection reformat image from post-contrast arterial-phase (WL: 256, WW: 771) shows absent opacification of the cortical segments of the middle cerebral arteries; these findings exclude the diagnosis of brain death according to the 10- and 7-point scales but confirm brain death on the 4-point scale in the A_0-V_{50} method. **d** Coronal maximum-intensity projection reformat from the venous phase (WL: 222, WW: 445) shows opacification of the cortical segments of the middle cerebral arteries; this finding excludes the diagnosis of brain death according to the 4-point scale in the $A_{50}-V_{50}$ method. Internal cerebral and the great cerebral veins were opacified (not shown). WL window level, WW window width



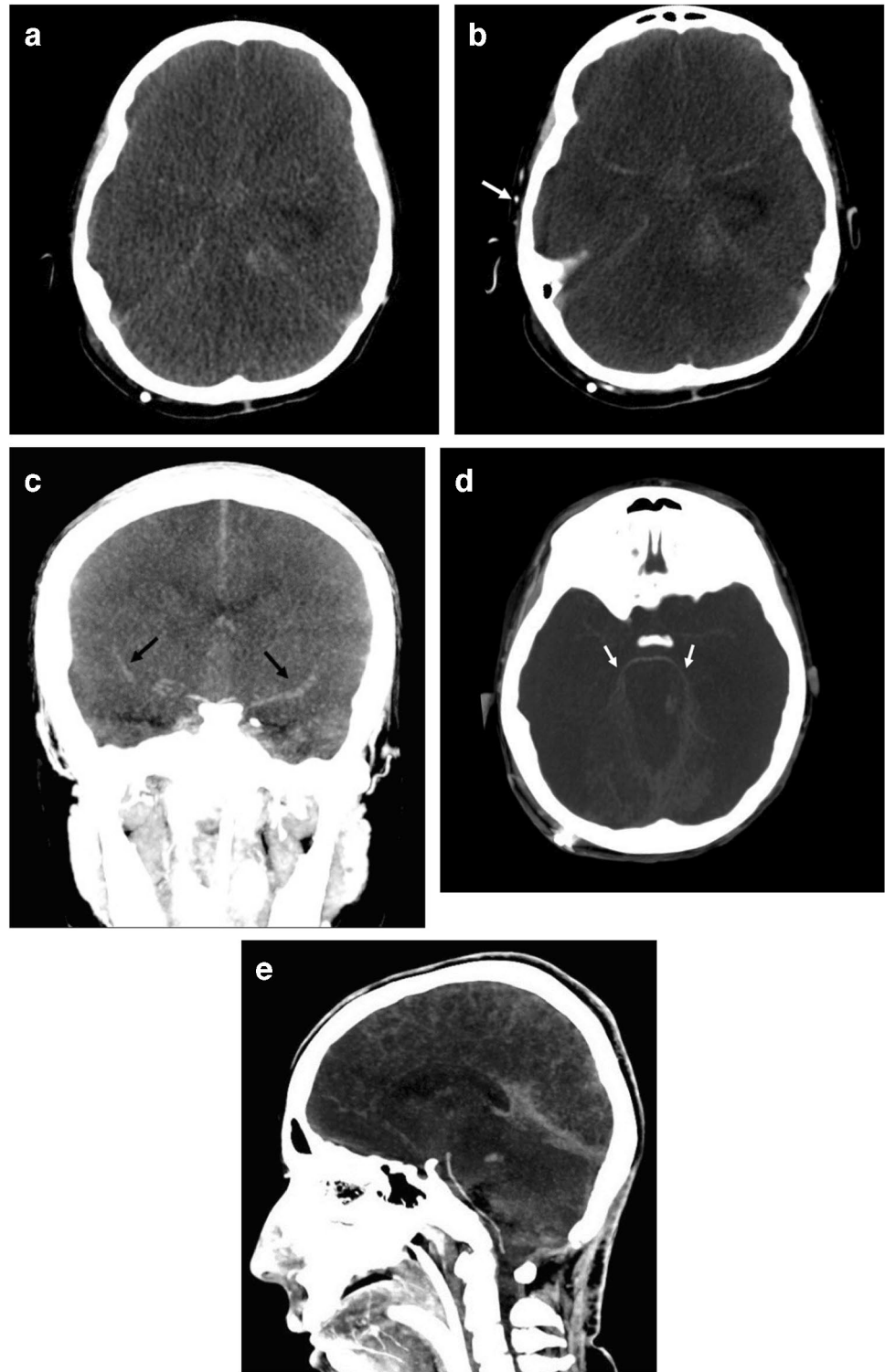
the 4-point scoring system to be in the range of 85% to 90%, similar to our study. Despite this, some authors have argued that the 4-point scoring system contradicts the definition of brain death in that it evaluates only the flow in the anterior circulation [1, 24], whereas brain death means irreversible function loss in all brain parts including the brainstem, not just the cerebrum.

Regarding the 7-point system, Quesnel et al. [2] compared EEG and CT angiography for the diagnosis of brain death in adults and found that the 7-point scoring system had a sensitivity of 52% in evaluation of the vessels in venous phase. Frampas et al. [10] compared 7- and 4-point scoring systems and calculated a sensitivity level of 63% for the 7-point scoring system in the evaluation of vessels in the venous phase. Sawicki et al. [5] compared 10-, 7- and 4-point scoring systems and observed a sensitivity level of 74% for 7-point scoring. Finally, Şahin and Pekçevik [4] compared the sensitivities of 10-, 7- and

4- point scoring systems and calculated the sensitivity of the 7-point scoring system as 64% in evaluation of the arteries in arterial phase and veins in venous phase [4]. In the present study, the sensitivity of the 7-point scoring system was higher (82% in $A_{50}-V_{50}$ method and 88% in A_0-V_{50} method) than the other studies. However in our study the interobserver reliability of the 7-point scoring system evaluated using the $A_{50}-V_{50}$ method was lower than those of other scoring systems.

While Sawicki et al. [5] and Şahin and Pekçevik [4] observed basilar artery opacification as 17% and 28%, respectively, we observed 22% opacification in the arterial phase and 56% opacification in the venous phase for the basilar artery. Şahin and Pekçevik calculated posterior cerebral artery P2 opacification as 12%, and we found this to be 19% in arterial phase and 37% in venous phase in our study. Combes et al. [12] reported that basilar artery and posterior cerebral artery P2 were not opacified in any cases.

Fig. 3 CT angiography findings in a 13-year-old girl. **a** Axial pre-contrast image (WL: 66, WW: 142) shows sulcal effacement and loss of gray–white matter differentiation. **b** Axial post-contrast arterial-phase image (WL: 80, WW: 154) shows opacification of superficial temporal artery (*arrow*), which indicates adequate technique. **c** Coronal maximum-intensity projection reformat from post-contrast venous-phase image (WL: 60, WW: 99) shows opacification of the proximal middle cerebral arteries (*arrows*) but absence of opacification of the middle cerebral artery cortical branches. **d** Axial maximum-intensity projection reformat from post-contrast venous-phase image (WL: 160, WW: 376) shows opacification of the posterior cerebral artery P2 segments. This finding excludes the diagnosis of brain death according to the 10-point scale but confirms brain death on the 7- and 4-point scales. **e** Venous-phase sagittal maximum-intensity projection image (WL: 80, WW: 116) shows no enhancement in the anterior cerebral artery. This girl was diagnosed with brain death both clinically and radiologically. WL window level, WW window width



The opacification of the posterior cerebral artery and basilar arteries shows significant variability in studies obtained with different protocols. Consequently, when our study was compared to other studies and evaluated within itself using different methods, the sensitivities of the 10-point scoring systems differed significantly.

In terms of the vascular structures evaluated in the scoring system, the lowest opacification in arterial phase was observed in the middle cerebral artery M4 and anterior cerebral artery A3, while the internal cerebral vein, great cerebral vein, anterior cerebral artery A3 segment and middle cerebral artery M4 segment had the lowest level of opacification in the

Table 6 Sensitivities of the 10-, 7- and 4-point scoring systems according to A_0 - V_{50} and A_{50} - V_{50} methods

Scoring system	A_0 - V_{50} method <i>n</i> (%)	A_{50} - V_{50} method <i>n</i> (%)
4-point	46 (92)	41 (82)
7-point	44 (88)	41 (82)
10-point	35 (70)	20 (40)

venous phase. Contrary to our findings, Sawicki et al. [5] and Şahin and Pekçevik [4] observed higher levels of opacification in the anterior cerebral artery A3 compared to posterior cerebral artery P2 in the venous phase.

In our study, we observed lower anterior cerebral artery opacification, so the sensitivity of the 7-point scoring system was higher compared to other studies in the literature. Interobserver reliability of the 7-point scoring system was also lower than that of both the 4- and 10-point scoring systems. This might

Table 7 Sensitivities of the 10-, 7- and 4-point scoring systems according to age group in the A_0 - V_{50} and A_{50} - V_{50} methods

Age group	4-point scoring		7-point scoring		10-point scoring		Total <i>n</i> (%)
	A_0 - V_{50} <i>n</i> (%)	A_{50} - V_{50} <i>n</i> (%)	A_0 - V_{50} <i>n</i> (%)	A_{50} - V_{50} <i>n</i> (%)	A_0 - V_{50} <i>n</i> (%)	A_{50} - V_{50} <i>n</i> (%)	
≤ 2 years	13 (87)	11 (73)	11 (73)	11 (73)	8 (53)	3 (20)	15 (30)
> 2 years	33 (94)	30 (86)	33 (94)	30 (86)	27 (77)	17 (49)	35 (70)

Table 8 Sensitivities of the 4-point scoring system in children whose bone integrity was preserved, whose anterior fontanelle was open and who had a craniotomy–craniectomy defect^a

Bone integrity	Number of patients	A_0 - V_{50} method		A_{50} - V_{50} method	
		Number of children with brain death diagnosis	Sensitivity	Number of children with brain death diagnosis	Sensitivity
Intact skull	13	13	100%	12	92%
Craniotomy–craniectomy defect	26	24	92%	22	85%
Anterior fontanelle open	8	7	88%	6	75%

^a Three children who had both craniotomy–craniectomy defect and open fontanelle were not included here

Table 9 Sensitivities of the 7-point scoring system in children whose bone integrity was preserved, whose anterior fontanelle was open and who had a craniotomy–craniectomy defect^a

Bone integrity	Number of patients	A_0 - V_{50} method		A_{50} - V_{50} method	
		Number of children with brain death diagnosis	Sensitivity	Number of children with brain death diagnosis	Sensitivity
Intact skull	13	13	100%	12	92%
Craniotomy–craniectomy defect	26	24	92%	22	85%
Anterior fontanelle open	8	6	75%	6	75%

^a Three children who had both craniotomy–craniectomy defect and open fontanelle were not included here

Table 10 Sensitivities of the 10-point scoring system in children whose bone integrity was preserved, whose anterior fontanelle was open and who had a craniotomy–craniectomy defect^a

Bone integrity	Number of patients	A_0 - V_{50} method		A_{50} - V_{50} method	
		Number of children with brain death diagnosis	Sensitivity	Number of children with brain death diagnosis	Sensitivity
Intact skull	13	10	77%	6	46%
Craniotomy–craniectomy defect	26	20	77%	12	46%
Anterior fontanelle open	8	4	50%	1	13%

^a Three children who had both craniotomy–craniectomy defect and open fontanelle were not included here

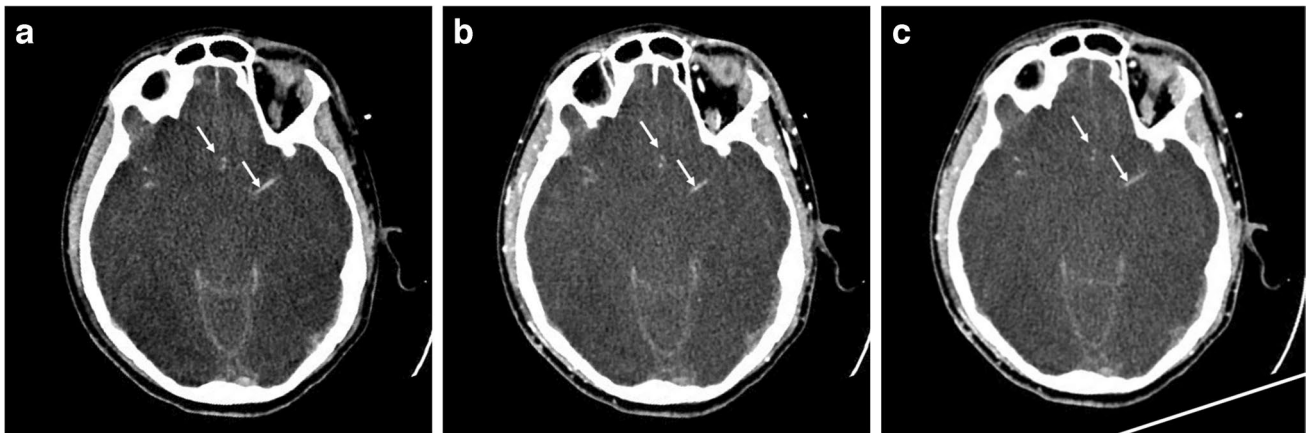
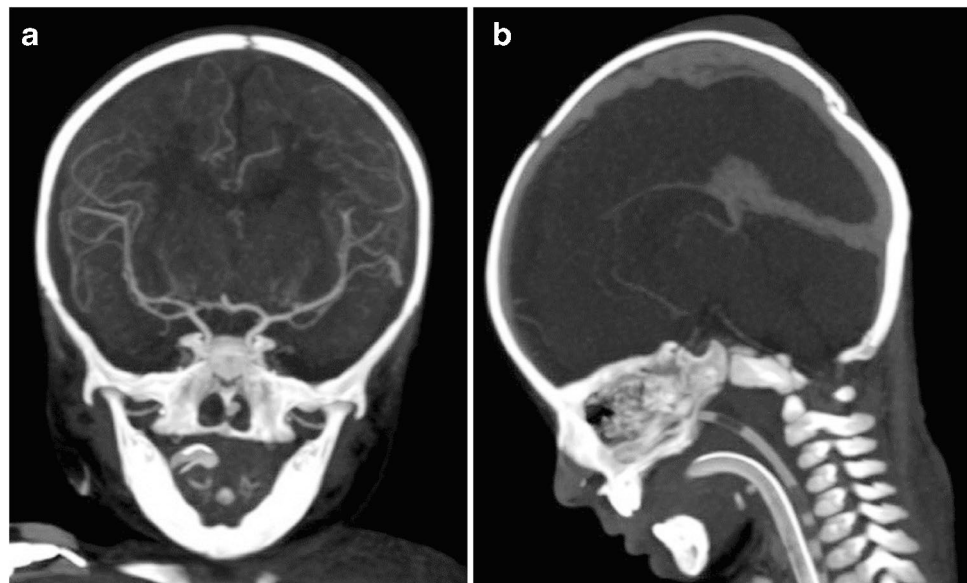


Fig. 4 Pseudo-subarachnoid hemorrhage sign in a 15-year-old boy. **a–c** Axial CT angiography. Pre-contrast image (WL: 46, WW: 80) (**a**), post-contrast arterial-phase image (WL: 48, WW: 110) (**b**) and post-contrast venous-phase image (WL: 46, WW: 114) (**c**) show simi-

lar opacification in anterior cerebral artery and middle cerebral artery tracts (*arrows*), which indicates pseudo-subarachnoid hemorrhage sign. This boy was diagnosed both clinically and radiologically with brain death. WL window level, WW window width

Fig. 5 Arterial opacification in a 6-month-old boy. **a, b** CT angiography. Coronal maximum-intensity projection (WL: 128, WW: 256) (**a**) and sagittal maximum-intensity projection reformat from post-contrast arterial phase (WL: 128, WW: 256) (**b**) images show opacification of the anterior cerebral, middle cerebral and basilar arteries. This finding excludes the diagnosis of brain death according to the 10-, 7- and 4-point scales. WL window level, WW window width



be because the anterior cerebral artery diameter is thinner than that of the middle cerebral and basilar arteries, as stated in the literature [25]. We should also consider that, especially in younger children, the cerebral parenchymal hypodensity might aggravate the appearance of pseudo-subarachnoid hemorrhage and this might complicate the identification of even thinner vessels.

Apart from these scoring systems, some authors include the superior petrosal vein in the evaluation, creating different scoring groups with higher sensitivity [3, 14, 15]. Because of the difficulty of evaluating pediatric patients, we did not include the superior petrosal vein in the present study. Similar to our findings, some authors also evaluated arterial structures in the arterial phase and obtained higher sensitivity [15, 19].

Some authors suggest that sensitivity can be increased by evaluating the arteries in the early phase because of the effects of (1) stasis filling from collateral circulation and retrograde intracranial venous drainage and (2) the pseudo-subarachnoid hemorrhage appearing more prominent in late phases [1, 19]. In this context, Nunes et al. [19] observed that the 4-point system had a sensitivity of 85% in the evaluation of arteries in the venous phase and 94% in the evaluation of arteries in the arterial phase. We obtained similar results in our study, with sensitivities of 82% and 92%, respectively.

Some authors suggest evaluation in the late phase because vascular opacification might be delayed by increased intracranial pressure [26]. Although the sensitivity is higher in

the arterial phase evaluation, it could be more appropriate to evaluate in the venous phase to reduce the risk of false positivity given that high specificity is more important than high sensitivity in the diagnosis of brain death.

In the pathophysiology of brain death, vasogenic and cytotoxic edema in the brain parenchyma under hypoxic and ischemic conditions causes an increase in intracranial pressure, resulting in decreased diastolic pressure, disappearing cerebral perfusion and finally, complete cerebral circulatory arrest [1, 6]. Therefore, defects in bone structure, ventricular drainage and open fontanelles can balance intracranial pressure increase up to a point, in which case clinical brain death diagnosis could be made, but this might not be reflected on CT angiography examinations [20, 26]. However, a time comes when intracranial pressure exceeds the arterial pressure, at which point intracranial blood flow is not observed despite the calvarial defects [22]. In 2019, Nunes et al. [19] compared patients with brain death diagnosis plus skull defects to brain death patients with no skull defects using the 4-point scoring system with arteries evaluated in the venous phase; they found a sensitivity of 76% in patients with skull defects and 95% in those without skull defects. In fact, when the same patients' arteries were evaluated in the arterial phase, the sensitivity levels were 89% and 100%, respectively [19]. In our study, we observed comparable sensitivity levels of 78% and 92%, respectively, using the $A_{50}-V_{50}$ method. Similarly, in the A_0-V_{50} method, we observed 89% sensitivity in the group with skull defects and 100% sensitivity in the group without skull defects.

Bone integrity was maintained in 13 of the 50 children in our study, while only a craniotomy–craniectomy defect was present in 26 children, only open anterior fontanelle in 8 children and both open anterior fontanelle and craniotomy–craniectomy defect in 3 children. A separate evaluation of these patient groups according to the 10-, 7- and 4-point scoring systems with both A_0-V_{50} and $A_{50}-V_{50}$ methods showed that the sensitivity was much lower in children with open anterior fontanelle compared to other groups. This can be explained by the ability of open sutures and anterior fontanelles to buffer increased intracranial pressure up to a certain limit [22]. When comparing age groups, we found the sensitivities of the scoring systems to be lower in children ≤ 2 years old and we suppose that this is related to their open fontanelles and sutures. However, it should be noted that, as is the case of blood pressure, normal intracranial pressure in young children is very low compared to adults, and therefore small increases in intracranial pressure can cause them more serious consequences [27, 28].

The present study has some limitations. First, we considered the clinical examination, including the apnea test, as the definitive diagnosis, but we had no idea whether the clinical diagnosis was performed correctly without a confounding element. Second, we did not compare the

results with another confirmatory test. Third, some of the children had pseudo-subarachnoid hemorrhage and subarachnoid hemorrhage findings. Because we could not perform subtraction in our clinic, we had difficulty evaluating the opacification of already thin vascular structures. Fourth, all children who underwent CT angiography had been clinically diagnosed with brain death, so we could not evaluate the specificity because there were no true-negative or false-positive patients. Fifth, we could not get data about the time interval between the clinical diagnosis of brain death and the CT angiography examination that was performed for each child. For the contrast agent flow to stop at the base of the head level, the intracranial pressure must exceed the mean arterial pressure. Given that brain death is a dynamic process, intracranial pressure might not exceed mean arterial pressure in the early stage, and in such cases cessation of intracranial circulation in all vascular areas might not be confirmed [20, 22]. Therefore, some guidelines recommend a 6-h interval between clinical diagnosis and CT angiography [22]. On the other hand, sensitivity would decrease in CT angiography examinations performed more than 12 h after clinical diagnosis [18].

Although the diagnosis of brain death is clinical, in some cases ancillary tests might be needed. Of these tests, CT angiography is frequently preferred because it is fast, easily accessible, noninvasive and less operator-dependent compared to cerebral angiography and it provides anatomical information. No consensus has been reached over the evaluation of CT angiography. Besides the various scoring systems, some authors argue that arteries should be evaluated in the arterial phase while others find that arteries should be evaluated in the venous phase. Moreover, more studies are needed concerning the child age group, which is physiologically different from adults.

Conclusion

To the best of our knowledge, the present study is the first to evaluate CT angiography examination for the diagnosis of brain death in the pediatric age group alone. We obtained similar results to those in other studies, especially regarding the 4-point scoring system. Because the scoring systems have similar sensitivities, we think they could be used as ancillary tests in pediatric cases. We prefer the use of the 4-point scoring system in pediatric patients because the 10-point scoring system (especially in children with open anterior fontanelle) had the lowest sensitivity and the 7-point scoring system had the lowest interobserver agreement in our study. In addition to having the highest sensitivity, we consider the 4-point scoring system to be more practical for evaluating vessel opacification by CT angiography. We think

that vascular opacification secondary to increased intracranial pressure might be delayed and therefore the A_{50} – V_{50} method is more suitable to use. However, we emphasize that CT angiography is not diagnostic alone because we do not have enough data about specificity. Carrying out CT angiography studies with larger pediatric patient groups and evaluating varying scoring systems and varying vascular structures could pave the way for more routine use of CT angiography as an ancillary test for the diagnosis of brain death in pediatric patients.

Declarations

Conflicts of interest None

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