Clinical Neurology and Neurosurgery 185 (2019) 105465

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Brain death: Radiologic signs of a non-radiologic diagnosis

Joseph Gastala[a,*], Deema Fattal[b], Patricia A. Kirby[b], Aristides A. Capizzano[c], Yutaka Sato[b], Toshio Moritani[c]

[a] Northwestern University, Department of Radiology, 676 N St Clair, Chicago, IL, 60611
[b] University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, IA 52242
[c] University of Michigan, 1500 E Medical Center, Dr Ann Arbor, MI 48109

ARTICLE INFO

Keywords:
Brain death
MR angiography
CT angiography
CT perfusion
Ancillary testing

ABSTRACT

Brain death is a clinical diagnosis characterized by the irreversible loss of neurologic function caused by global injury to the brain, including the brain stem. This is often caused by trauma and subarachnoid hemorrhage amongst other etiologies. This injury results in extensive cerebral edema, a rise in intracranial pressure, and eventual cessation of cerebral blood flow. Although brain death is a clinical diagnosis, ancillary and confirmatory tests are widely used. These are categorized into imaging that demonstrates absence of cerebral blood flow and electroencephalography that demonstrates absence of cortical electrical activity. Cerebral angiography, transcranial Doppler, and cerebral scintigraphy are the only imaging studies to have been validated by the American Academy of Neurology for diagnosis of brain death. However, characteristic findings on computed tomography, computed tomography perfusion, computed tomography angiography, magnetic resonance imaging, and magnetic resonance angiography may suggest the diagnosis. In this article, the clinical criteria, pathophysiology, pathology, and variations in current practice of brain death diagnosis are discussed, and the imaging findings of brain death are reviewed.

1. Introduction

The concept of brain death was first described by Mollaret and Goulon in 1959 when they described “le coma dépassé” of comatose patients supported by mechanical ventilators with absent electroencephalographic (EEG) recordings, absent intracranial flow, or total brain necrosis at autopsy [1]. Before the advent of artificial cardiopulmonary support and mechanical ventilation, loss of heart and lung function were easily observable and sufficient to diagnose death. With the capability to maintain vital body functions after the brain had irreversibly ceased to function, a reexamination of the criteria of death followed [2].

In 1968, an ad hoc committee at Harvard Medical School expanded the medical definition of death based on neurologic criteria, defined as loss of function at the cerebral and brain-stem levels characterized by unresponsiveness and lack of receptivity, absence of movement and breathing, absence of brain-stem reflexes, a flat EEG, and by coma whose cause was known [2]. This effort was spurred by the moral, ethical, and legal controversies of organ transplantation in patients with irreversible coma and futile attempts at continued life support [2]. In the United States (US), the Uniform Determination of Death Act in 1981 provided a new legal and medical basis for defining death based on both cardiopulmonary and neurologic criteria [3]. Brain death was defined as the “Irreversible cessation of functions of the entire brain, including the brain stem.”

Early recognition of brain death is important to expedite organ transplantation, provide closure for loved ones, and prevent futile medical interventions [4]. It comprises 1%–2% of deaths yearly in the US [5] and, in a large referral hospital, it may be diagnosed from 25 to 30 times per year [6]. The diagnosis of brain death is inherently a clinical diagnosis that is not always straightforward. In the US, the American Academy of Neurology (AAN) has promulgated the American Academy of Neurology Practice Parameters (AANPP) for the determination of brain death, first in 1995 and with an update in 2010, to establish guidelines and provide uniformity for the diagnosis [7]. Certain ancillary tests (electroencephalography [EEG], angiography, transcranial Doppler [TCD], and scintigraphy) have been validated by the AAN to be used as confirmation in situations of uncertainty although ancillary testing remains controversial. Although brain death is a clinical diagnosis, radiologists may encounter it with ancillary testing and

* Corresponding author.
E-mail addresses: jgastala@gmail.com (J. Gastala), deema-fattal@uiowa.edu (D. Fattal), patricia-kirby@uiowa.edu (P.A. Kirby), capizzan@med.umich.edu (A.A. Capizzano), yutaka-sato@uiowa.edu (Y. Sato), tmoritan@med.umich.edu (T. Moritani).

https://doi.org/10.1016/j.clineuro.2019.105465
Received 21 June 2019; Received in revised form 30 July 2019; Accepted 6 August 2019
Available online 12 August 2019
0303-8467/

imaging modalities including computed tomography (CT), CT angiography (CTA), CT perfusion (CTP), magnetic resonance imaging (MRI) including diffusion-weighted imaging (DWI), and magnetic resonance angiography (MRA) and must be familiar with the diagnosis. In this article, we review the clinical criteria and diagnosis of brain death, discuss the pathology and pathophysiology, and discuss the key imaging findings that can suggest and aid in the diagnosis.

2. Pathogenesis and pathology of brain death

The inciting event of brain death is global irreversible injury to the brain [8]. In most adult series, traumatic brain injury and subarachnoid hemorrhage are the most common intracranial events leading to brain death [9,10]. In the intensive care unit, it is most commonly seen with large ischemic strokes or anoxic encephalopathy, often caused by an extracranial event such as cardiopulmonary arrest, resulting in prolonged and severe impairment of blood supply to the brain [5,8]. Any acute large space occupying lesion with brain herniation and compression of the brain stem can also cause brain death. Whatever the etiology, eventually global cerebral injury leads to marked brain swelling and destruction of brain parenchyma despite continued advanced life support. The most common mechanistic pathway leading to brain death is increasing intracranial pressure to the point of cessation of intracranial blood flow [11,12].

As a result of the inciting event, alterations in blood flow as well as oxygen and glucose supply leads to local or global injury [5]. Depending on the nature of the inciting event, there is increasing brain edema which can be intracellular (cytotoxic) secondary to hypoxia and changes in osmolar regulation [5] or extracellular (vasogenic) secondary to disruption of the blood brain barrier and loss of autoregulation [13]. As the brain is confined to a rigid structure, the cranium, there is limited ability to compensate for the increasing brain volume as edema progresses [14].

The main compensatory process for maintaining constant intracranial pressure (ICP) is CSF reduction, primarily by CSF resorption [14]. Once compensatory mechanisms are overcome, ICP rises and cerebral perfusion pressure decreases (Fig. 1). A threshold is finally reached at which small increases in brain volume lead to exponential rises in ICP [15].

When the volume of the expanding brain exceeds the skull volume, brain herniation will occur [13]. This causes compression and eventual irreversible damage to the brainstem leading to disruption of respiratory and cardiac centers as well as the reticular activating system [5], and this injury leads to loss of brainstem reflexes [16]. Respiratory failure from brainstem compression further exacerbates hypoxia and causes further increases in ICP[13]. When ICP exceeds arterial perfusion pressure, intracranial circulation ceases [14,15]. Subsequently, loss of physiologic brain activity and electrocerebral silence are irreversible in the setting of brain death [17].

Post mortem examination of the brains of patients with irreversible brain injury can show uncal, central, and tonsillar herniations. This leads to compression of the brainstem with stretching and tearing of pontine perforating branches of the basilar artery resulting in pontine Duret hemorrhages (Fig. 2a). The brain is congested, soft to friable in texture, and has a dusky appearance [18] (Fig. 2b). Microscopy shows global cytotoxic and interstitial edema with diffuse neuronal ischemic-anoxic injury (Fig. 2c).

In the past, cerebral pathology of brain dead patients was referred to as “respiratory brain” with a dusky congested brain and extensive brain damage; the brain often was very friable upon removal from the skull [18–20]. In the modern era, with time to death and brain at autopsy shortened due to organ donation protocols, brain pathology is currently done within days of brain death diagnosis and the resulting pathology is different from the so-called respirator brain. The pathological findings in the modern era can be nonspecific and without pathognomonic features as previously recognized. More importantly, there may be lack of uniformly severe pathology. For example, Wijdicks found mild changes in one third of cerebral hemispheres and in one half of brainstems in brains studied within 36 hours of declaration of brain death [21].

3. Diagnosis

Brain death is a clinical diagnosis that can only be determined when the clinical situation meets specific prerequisites [22]. First, there must be clinical or neuroimaging evidence of an acute catastrophic event that could cause clinical brain death; this is commonly demonstrated on CT scanning. Secondly, complicating medical conditions that may confound clinical assessment must be excluded, including severe acid-base disturbances, electrolyte imbalances, or endocrine disturbances. These must be investigated even if there is an abnormality discovered on imaging. Third, there must be no drug intoxication or poisoning. Finally, hypothermia must be excluded, and the core temperature must be greater than 36 °C.

Once these prerequisites are met, clinical examination is appropriate. The diagnosis of brain death is made with documentation of the three cardinal findings: coma, absence of brain-stem reflexes, and apnea (Table 1) [8]. Coma is assessed by performing a complete neurological examination in accordance with the AAN guidelines [8], which includes testing for absent responses to verbal, visual and painful stimuli on the face and extremities. Absence of brain-stem reflexes is assessed by examining the pupils, ocular movements, facial motor response, and

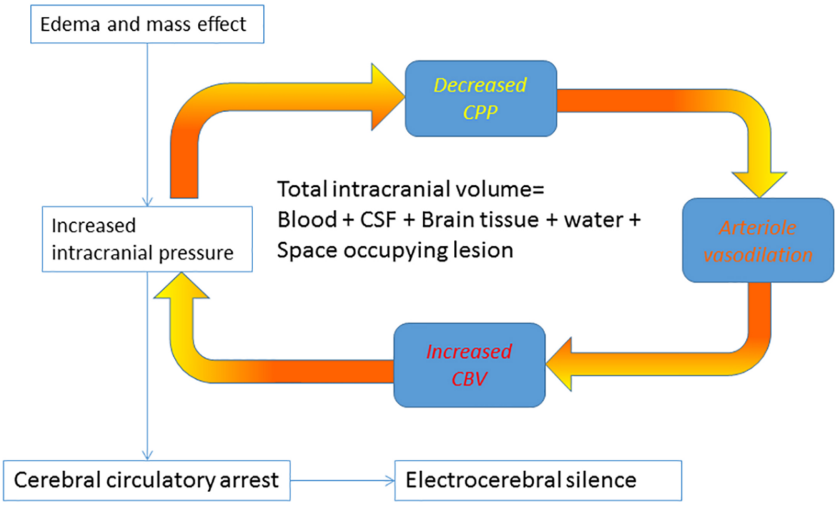

Fig. 1. Intracranial pressure and intracranial volume regulation. Total intracranial volume is comprised of the volume of the cerebrospinal fluid (CSF), the brain, intracellular and extracellular water, blood volume and any volume contributed by a possible tumor, hematoma or other mass lesion (8, 12). An increase in any one of these components must be accompanied by a decrease in another. Increasing intracranial pressure (ICP) causes arteriolar vasodilation to maintain cerebral perfusion pressure (CPP) also resulting in increased cerebral blood volume (CBV). CPP is the driving arterial pressure gradient across cerebral vasculature demonstrated by the following relationship: CPP = Mean arterial pressure (MAP)–ICP (9). With decreasing CPP, arterial vasodilation occurs to maintain cerebral blood flow in a process called autoregulation. However, this vasodilation leads to increased cerebral blood volume (CBV), and a vicious cycle may occur in which further rises in CBV cause further increases in ICP (9).

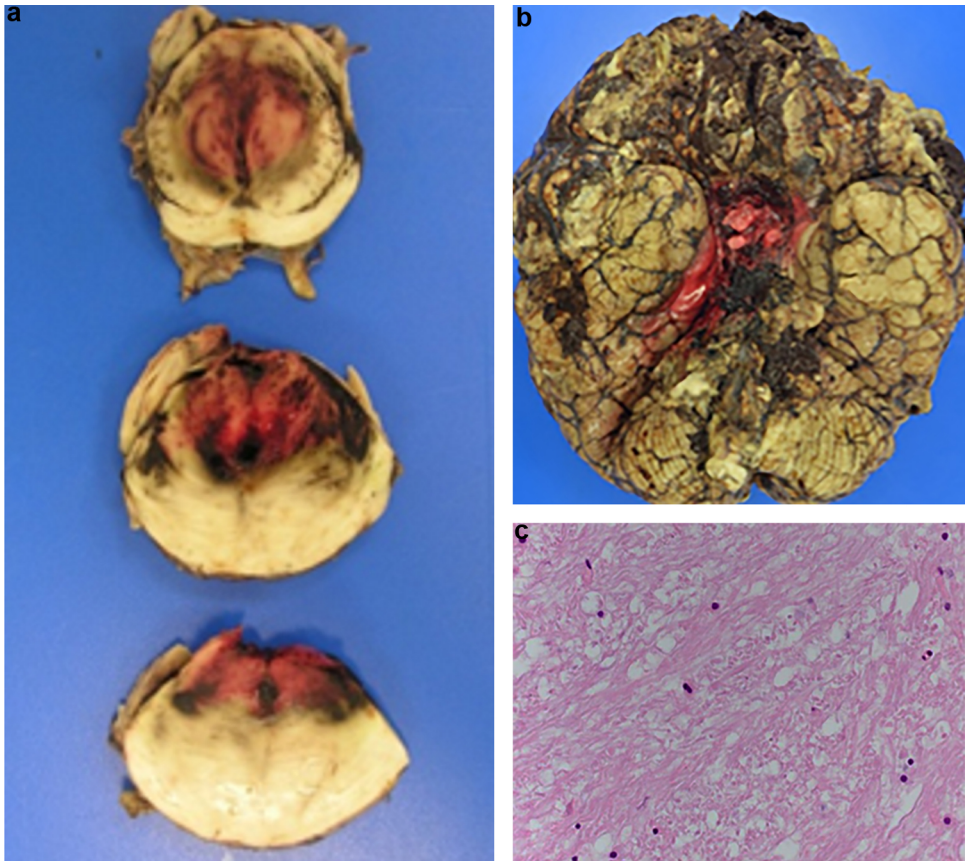

Fig. 2. Gross pathology and microscopy in cases of clinically diagnosed brain death.
(a) Duret hemorrhages after compression of the brainstem.
(b) The brain increasingly takes on a dusky, congested, and discolored appearance.
(c) Microscopy demonstrates cytotoxic edema in the brain stem with vacuolation of the white matter neuropil (hematoxylin-eosin stain, original magnification ×400)

Table 1
Brain death diagnostic criteria [8].

Clinical Criteria
Absence of motor responses to painful stimulus
Absence of response to supraorbital nerve pressure, temporomandibular joint pressure, sternal rub, or nail-bed pressure
Absence of brain stem reflexes
Absence of pupillary responses, corneal reflexes, caloric responses, gag reflexes, coughing in response to tracheal suctioning, sucking and rooting reflexes
Apnea
Absence of respiratory drive
Validated confirmatory tests
Confirmation of loss of electrical activity
Electroencephalography
Demonstration of loss of cerebral blood flow
Cerebral angiography
Transcranial Doppler ultrasonography
Cerebral scintigraphy

pharyngeal and tracheal reflexes [8]. Finally, a positive apnea test is the absence of breathing when the PaCO2 reaches a target level of 60 mmHg or increases 20 mmHg above the baseline after 8–10 min of disconnection from the ventilator [8,23]. The key distinction between adult and pediatric brain death determination is the addition of a second, confirmatory examination including apnea testing 12 to 24 hours after the initial examination with pediatric patients [24].

If specific components of the clinical testing or the apnea test cannot be reliably evaluated, or are inconclusive, confirmatory and ancillary testing can assist in the diagnosis. The most common indication confirmatory testing is performed is the failure to complete the apnea test [22] and other indications include situations in which cranial nerves cannot reliably be assessed, such as in patients with skull base or facial trauma or patients with pre-existing cranial neuropathies [17]. Ancillary tests can lead to false-positive (ancillary test suggests brain death but the patient does meet clinical criteria) or false-negative results (clinical brain death but confirmatory test is negative) [22] (Tables 2 and 3).

Ancillary tests can be divided into tests that evaluate brain function, such as EEG, and tests that evaluate intracranial blood flow, such as imaging studies [17]. The tests which have been investigated, validated, and approved by the AAN are cerebral angiography, TCD, and cerebral scintigraphy [8]. The decision to use a specific ancillary test is dependent on many factors, including availability, safety of transport, and diagnostic accuracy [25] and there is no evidence to support use of one ancillary test over another. Further research would be helpful to establish guidelines in this regard if ancillary testing is used. The most specific confirmatory findings on imaging are related to the cerebral circulatory arrest caused by increased ICP [26], with loss of CBF.

4. Variations in clinical practice

There is no international consensus for the diagnosis of brain death and the role of ancillary testing as there are wide variations in guidelines and legislation [17,27]. Even though the lack of uniformity in brain death determination has improved over time [7] discordant practices still abound [28–30]. Some advocate the diagnosis can always be made clinically if the examination is performed properly and ancillary testing is unnecessary [22]. About half of European countries routinely require ancillary tests before brain death can be diagnosed [27]. Others require ancillary testing only when confounding factors interfere with the clinical determination [31]. In the US, there is no federal legislation regarding the determination of the diagnosis, and legal guidelines vary state by state [5,8]. In 2010, the AAN updated the AANPP with the attempt to standardize the diagnosis, and reiterated that the diagnosis of brain death can be made without ancillary testing, also highlighting the as of yet unproven role of newer ancillary methods such as CTA [7].

Table 2
Comparison of imaging modalities [17,25,39,42].

Modality		Technical Aspects	Findings	Advantages	Disadvantages	Potential Pitfalls
Cerebral Angiography		−Separate injections are performed in both common or internal carotid arteries as well as vertebral arteries	−Lack of opacification of intracranial ICAs and vertebral arteries	−Excellent for demonstrating intracranial blood flow −Validated by AAN -Considered “gold standard”	− Operator dependent − Limited availability − Contrast load − Radiation dose − Limited anatomic detail - Possible damage to transplant organs with vessel occlusion	−False positive in hypotensive patients -Stasis filling
Cerebral Scintigraphy		−Tc-99 HMPAO or ECD most commonly used -Up to 30 mCi radiotracer may be used	−Absence of cerebral uptake, cerebellar uptake, or both -Hot nose sign	-Validated by AAN	−No anatomic detail -Limited availability	-False negative in decompressive craniectomy or other reason for intracranial decompression
Transcranial Doppler		−2 MHz probe -Bitemporal and suboccipital acoustic windows are utilized	-Progressive loss of forward flow	−No radiation -Validated by AAN	−Operator dependent -Acoustic window may be limited	-False negative in decompressive craniectomy or other reason for intracranial decompression
MRI	Conventional	−May be performed on 1.5 T or 3 T magnet	−Transtentorial and foramen magnum herniation −Absent intracranial vascular flow voids −Poor white/gray matter differentiation -MR hot nose sign	−No radiation -Provides anatomic information	−Time consuming −Expensive −Not widely available −Difficult to perform on ventilated patients -Variable criteria for intracranial circulatory arrest	−MRI artifacts
	DWI		-Diffuse decrease in ADC extending to the brainstem			
	SWI/GRE		−Transcerebral and transcortical vein signs -Prominent medullary veins			
	MRA		-Lack of flow above supracliniod ICAs, no contrast distal to level of ACA and M1 segment of MCA			
CT	Noncontrast	−Protocol typically includes noncontrast CT brain, with 20 s arterial and a delayed 60 s venous phase	−Brain herniation patterns -Mass, hemorrhage, edema	−Widely Available −Rapid -Provides anatomic information	−Radiation dose −Contrast load with CTA/CTP -Variable criteria for intracranial circulatory arrest	−False positive in hypotensive patients −False negative in decompressive craniectomy or other reason for intracranial decompression -Stasis filling
	CTA		−Lack of opacification of ICVs is most sensitive -4 and 7 point scales for intracranial opacification			
	CTP		-Matched decrease in CBF and CBV extending to the brainstem			

Table 3
Sensitivity and specificity of imaging modalities[8,38,47,59–61,64,69,76–79].

Modality	Sensitivity/Specificity	Number of reported proven brain death patients	Number of reported non brain death patients with a positive result
Cerebral Scintigraphy	70–100%;97-100%	274; 226 positive, 48 negative	0
Transcranial Doppler	73–100%;75-100%	1311; 1137 positive, 174 negative	6
MRI/A	93–100%;100%	64; 59 positive[b], 5 negative	0
CTA	62–100%;NA[a]	467[c]; 391 positive, 76 negative	1[d]
CTP	86–100%;NA[a]	38; 35 positive, 3 negative	0

[a] All studies but one included only patients which were already clinically diagnosed with brain death. One study of 22 patients included a small number ($n = 2$) of patients which were not prospectively diagnosed with brain death.
[b] Positive result with no flow above supraclinoid ICA on MRA or loss of flow void on conventional MRI
[c] Includes studies only for which a 4 point scale could be determined, i.e. two phase exam with explicit examination of 4 point criteria.
[d] A case report of a patient unable to complete apnea testing. A CTA was positive for brain death, but a TCD 9 h following was negative. An HMPAO SPECT study 3 h of after the TCD was positive for brain death.

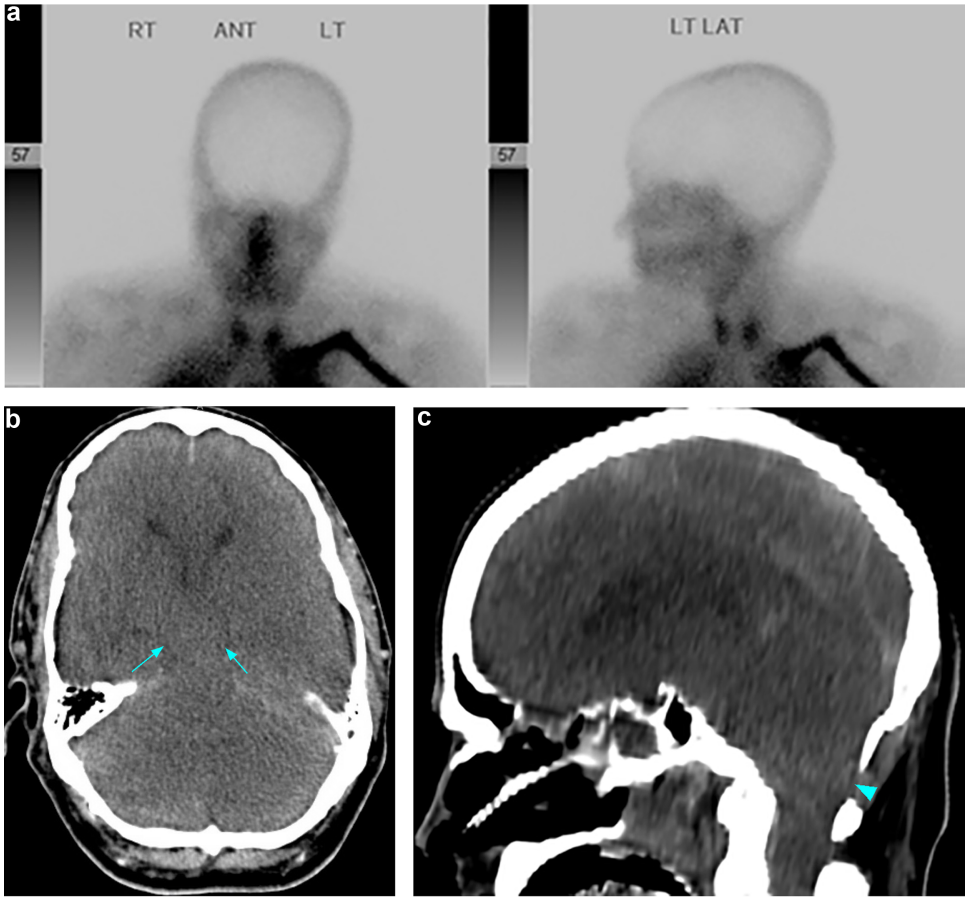

Fig. 3. Clinically diagnosed brain death in a 43-year-old male with aortic dissection, post-operative course complicated by ischemic bowel. **(a)** Tc-99 m HMPAO scintigraphy at the same day of the CT demonstrates no intracranial vascular flow.
(b, c) Axial and sagittal CTA images demonstrate bilateral transtentorial (arrows) and tonsillar herniation)(arrowhead). Note a lack of opacification of intracranial circulation with no opacification in the internal cerebral veins and middle cerebral arteries, findings that confirm brain death.

Actual practice patterns also vary widely despite some established guidelines. For example, in the US, despite guidelines established by AANPP 2010, a study of patients diagnosed with brain death over a one year period found that at least one ancillary test had been performed in about 65.5% of patients, with CTA being performed in 12.8% of those patients [28]. Therefore, despite the controversial and uneven role ancillary testing plays in the diagnosis, imaging is still widely used.

5. Imaging in brain death

5.1. Cerebral angiography

Cerebral angiography is considered the gold standard for assessment of intracranial circulation [32]. In the setting of brain death, flow is obstructed in the internal carotid and vertebral arteries due to increased ICP, and angiography will show no intracerebral filling at the level of entry of these arteries to the skull [33,34]. Destruction of the intracerebral vascular tree in conjunction with necrosis related to brain injury also contributes to the absence of intracranial flow.

The flow pattern in brain death is the reverse of the normal cerebral vascular filling, in which the low resistance intracranial arteries fill before the higher resistance extracranial arteries. In brain death, external circulation remains patent, filling rapidly and early. In certain patients, supratentorial circulation can cease but persistent and delayed posterior fossa blood flow can be seen, which may result from the protective effect of the cerebellar tentorium from increased hemispheric pressure [35].

Despite the advantages of accuracy and resolution, angiography is invasive, time-consuming, and dependent on the availability and skill of the operator. Additionally, angiography may inadvertently obstruct flow within the remaining vessels and cause damage to transplantable organs of brain death donors. Pitfalls can occur when the patient does

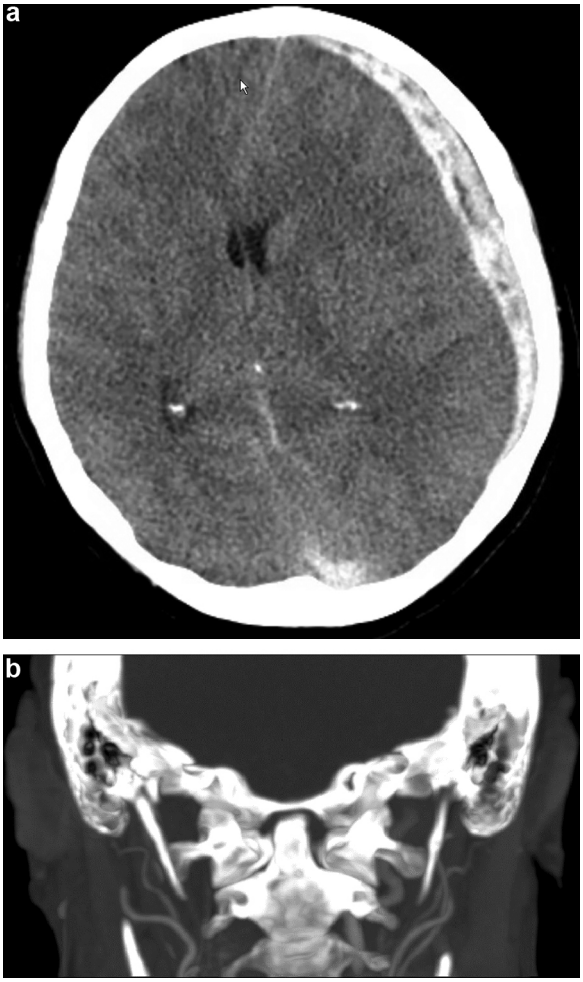

Fig. 4. 57-year-old female with brain death. Initially presented with headaches and subsequently became unresponsive. **(a)** Axial noncontrast CT demonstrates subdural hematoma with midline shift.
(b) Coronal CTA maximum intensity demonstrates external carotid artery branches and a lack of opacification of intracranial circulation.

not meet clinical criteria yet the cerebral angiogram is consistent with brain death (false positive test) [22], or, conversely, when there is persistence of intracranial circulation in the clinical setting of brain death, which has been documented in many case reports (false negative test) [36]. This persistence of blood flow in brain death can affect not only the interpretation of cerebral angiograms, but also other imaging methods (such as CTA and MRA) that evaluate cerebral blood flow and cerebral perfusion. One of the most common scenarios for this phenomenon is when the imaging study has been performed after clinical brain death, but before the ICP exceeds systolic pressure [36].

5.2. TCD sonography

TCD is inexpensive and noninvasive and can be performed at the bedside. It is a validated confirmatory test, with sensitivity varying from 91-99% and specificity of 100% [37]. A systematic review by Chang et al. showed pooled sensitivity and specificity of 90% and 98%, respectively, for showing cerebral circulatory arrest [38]. Moreover, sensitivity increases with time, reaching 100% after 36 h [22]. Yet, false positive and false negative results (using the clinical exam as reference) are well documented [22]. TCD in brain death shows cerebral circulatory arrest in the middle cerebral arteries, indicated by characteristic flow patterns without forward flow progress [37,39,40]. Disadvantages include operator dependence as well as dependence on the available acoustic window[41].

Cerebral scintigraphy

Multiple radiotracer uptake patterns have been described with cerebral scintigraphy in the setting of clinical brain death. Typical agents used include 99mTc hexamethylpropyleneamine ozime (HMPAO) or 99mTc ethylene cysteine diethyl ether (ECD) with planar or single photon emission CT (SPECT) [42]. Demonstration of no uptake within the cerebrum and cerebellum provides straightforward confirmation [43] (Fig. 3a). Another uptake pattern that has been described is the preservation of cerebellar perfusion without cerebral perfusion. All documented cases with this pattern have eventually been diagnosed with brain death, but this is still considered an equivocal finding [26,43]. A rare pattern is absent cerebellar but preserved cerebral uptake [44], which is also equivocal. The “hot nose” sign is another finding referring to increased uptake in the nasal area with nonfilling of intracranial arteries and can be seen with brain death [45,46]. As with the other ancillary tests, cerebral scintigraphy has significant false positive and false negative results when compared to the clinical exam [22,47].

5.3. CT

In patients suspected of brain death, initial interpretation of the noncontrast CT scan is essential in helping determine the underlying cause [48] (Fig. 4a). This may demonstrate single or multiple hemispheric lesions, intracerebral hemorrhage, stroke, tumor, or edema, corresponding to the initial inciting event. A positive finding on CT, however, still requires careful consideration of any confounding factors [48]. A negative CT scan should cast doubt on the diagnosis, although it still may be falsely normal in certain patients after cardiorespiratory arrest and acute stroke [9]. The noncontrast CT is of limited use beyond radiologic evaluation for an inciting cause, as brain edema, trauma, and ischemia can occur without clinical brain death.

5.4. CTA/CTP

CTA has gained attention in the evaluation of brain death as it is a non-invasive and widely available technique that clearly demonstrates contrast medium in the vascular system to evaluate cerebral circulation and is relatively less operator dependent than conventional angiography [49] (Fig. 3b-d). Several vessels have been proposed for the demonstration of intracerebral circulatory arrest in both arterial and venous phases [50–54]. Three-dimensional reconstruction images of CTA can demonstrate external carotid artery branches and a lack of opacification of intracranial circulation (Fig. 4b,c).

Multiphase spiral CTA provides both anatomical and functional information of brain death (Fig. 5a-c). In the seminal study by Dupas et al., 14 clinically brain dead patients were scanned in two phases: twenty seconds and then 54–60 s after initial injection [50]. Brain death diagnosis in this study relied on a score based on lack of opacification of 7 intracerebral vessels: the pericallosal arteries, cortical segments of the middle cerebral arteries (MCA), internal cerebral veins (ICV), and 1 great cerebral vein. Lack of opacification of these vessels indicated stagnation and arrest of contrast medium at the level of internal carotid and vertebral arteries with absence of venous blood return. There were 2 brain dead patients who had MCA M1 segment weak opacification, including one where angiography showed no flow (false negative). The specificity was 100%, as compared to CTAs of healthy volunteers used as controls. On the basis of this study, this was accepted as one of the ancillary tests for brain death diagnosis in France and Netherlands [49]. Additionally, Austria, Switzerland, and Canada adopted its use in confirmation of brain death, even though follow up studies did not replicate the results, with sensitivity ranging from 11 to 48% although

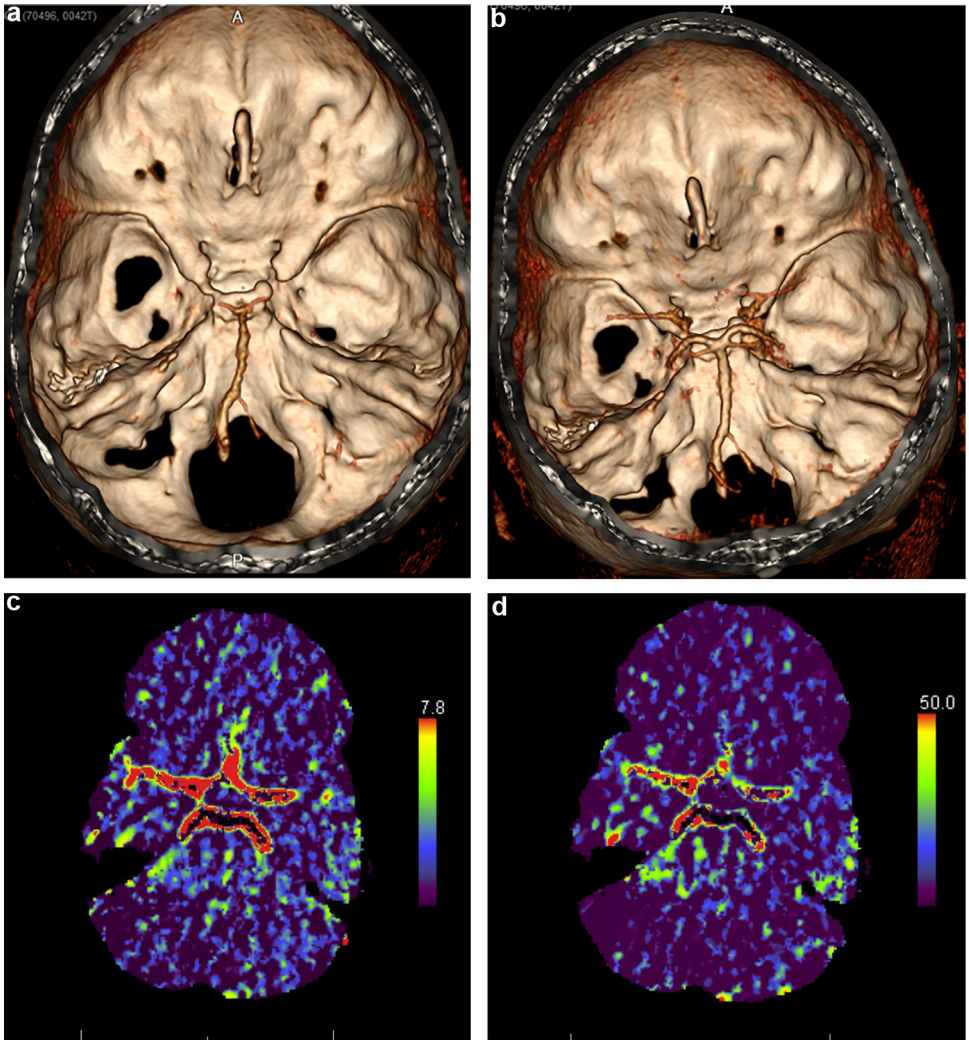

Fig. 5. 42-year-old female with brain death. Presented with diffuse subarachnoid hemorrhage. **(a, b)** Axial 3D multiphase CTA images demonstrate delayed opacification of intracranial circulation (**a**: 24 sec, **b**: 43 sec after contrast injection).
(c,d) CT perfusion images demonstrate matched and decreased CBV **(c)** and CBF **(d)** in the supratentorium and posterior fossa including the brain stem.

there was some variability in the diagnostic criteria and contrast phase timing [51–53].

Frampas et al. introduced a more simplified 4 point score based on lack of opacification of the cortical segments of the MCAs and ICVs [54]. The 4 point scale was more sensitive than the 7 point scale, with a sensitivity of 85.7% versus 62.8%, respectively. Subsequent studies have also found absence of opacification of the MCAs and ICVs to be more sensitive than the 7 point scale for demonstrating brain death [55,56].

CTP in addition to CTA, with a focus on the brain stem, may be useful as an additional ancillary tool [57] (Fig. 5d,e). This was demonstrated in a retrospective study of 11 patients by Shankar et al. that yielded a sensitivity of 100% with CT perfusion in addition to CTA, using criteria of no flow or matched CBF and CBV reduction within the brainstem. Comparatively, the sensitivity of both the 4 and 7 point scales in this study was 72.7% [57]. Another study by Escudero et al. of 27 patients showed a sensitivity of 89% using CTP and CTA [58]. These studies suggest that CTP in addition to CTA may increase sensitivity, but this needs to be validated on a larger scale.

Two systematic reviews have assessed the accuracy of CTA in the diagnosis of brain death [56,59], and another more recent systematic review has assessed CTA in addition to CTP [60]. In a Cochrane review by Taylor et al., the sensitivity in 8 studies involving 337 patients was low at 84% compared to clinical testing; when using only the 4-point scale, sensitivity was only 85%. Specificity could not be calculated as all brain dead patients were diagnosed with clinical assessment, and there were no patients for whom CTA was performed without the clinical diagnosis. The authors concluded that CTA “may be useful… assuming that clinicians are aware of the relatively low overall sensitivity” [56]. In a study by Kramer [59], the pooled sensitivity was 62% for venous phase and 84% for arterial phase imaging in 12 studies involving 541 patients when compared to clinical testing, cerebral angiography, or radionuclide imaging. The most recent systematic review by Brasil et al. revealed a sensitivity of 87.5% in 8 studies involving 322 patients using the 4 point scale but found no benefit for adding CTP based on 2 studies [60]. Given the low sensitivity in these systematic reviews, a substantial portion of cases would not be diagnosed as brain death. In all these studies performed, absence of opacification of the internal cerebral veins was the most sensitive parameter for the diagnosis of brain death [52,56,60], although none have evaluated ICV a priori for the diagnosis.

A major limitation in nearly all the previous studies is that all studied patients had already been diagnosed with clinical brain death and there was no inclusion of patients without the diagnosis. Therefore, specificity could not be determined on prior studies. A recent study by Garrett et al. is the first to include a control group of neurologically critically injured patients which did not meet the clinical criteria for brain death. While this control group was small ($n = 2$), the authors

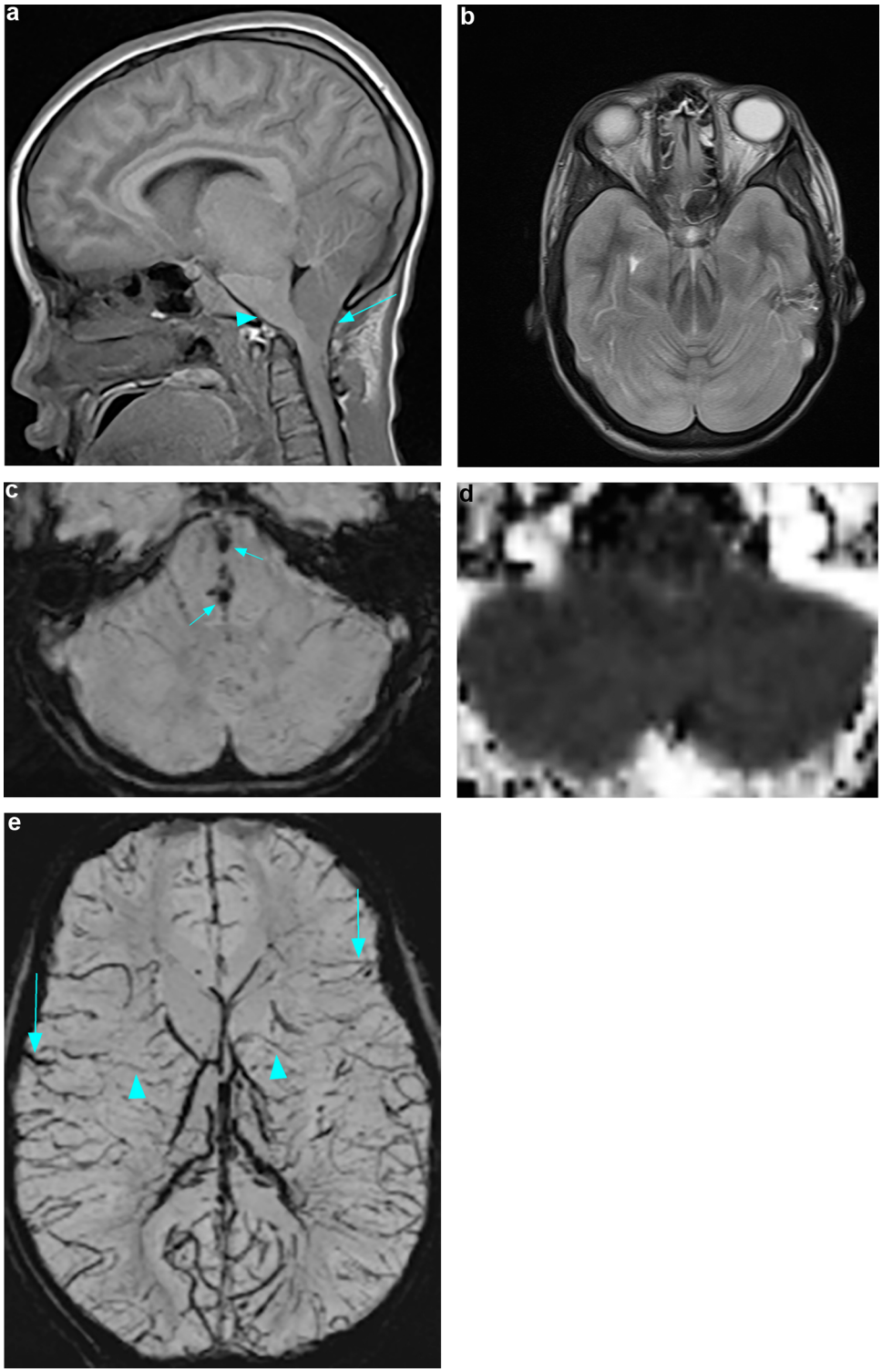

Fig. 6. Clinically diagnosed brain death after imaging in an 11-year-old female with anoxic brain injury. **(a)** Sagittal T1 weighted image demonstrates marked diffuse brain edema with tonsillar herniation (arrow) and brain sagging (arrowhead).
(b) Axial T2-weighted images at the level of the pons shows diffuse obliteration of cortical sulci and loss of flow voids within the bilateral ICAs (arrows).
(c) Axial susceptibility-weighted image demonstrates Duret hemorrhages in the center of the pons.
(d) Axial ADC map demonstrates prominently decreased ADC in the entire brain stem extending to the medulla (0.25×10^{-5} mm^2/sec) and cerebellum.
(e) Axial susceptibility-weighted image demonstrate transcortical (arrows) and transcerebral (arrowheads) vein signs with prominent medullary veins.

found a specificity and positive predictive value of 100% compared to the clinical exam using the 4 point scale [61].

Despite its advantages, CTA is not yet widely accepted as an ancillary test for the diagnosis of brain death with the main obstacle being insufficient diagnostic confidence [53]. There is also no consensus regarding the radiographic criteria used to demonstrate absence of intracranial blood flow [17]. One major limitation is persistent contrast enhancement of cerebral vessels, which could be interpreted as persistence of intracranial flow [53], as has been described with cerebral angiography. This can occur in patients who have had decompressing fractures or craniectomies, ventricular shunts, as well as brain herniation [36,62].

5.5. MRI/MRA

MRI can demonstrate some characteristic findings in the setting of brain death. Orrison et al. first identified 6 signs on MRI: 1) transtentorial and foramen magnum herniation, 2) absent intracranial vascular flow voids, 3) poor gray matter/white matter differentiation, 4) absent intracranial contrast enhancement, 5) carotid artery enhancement

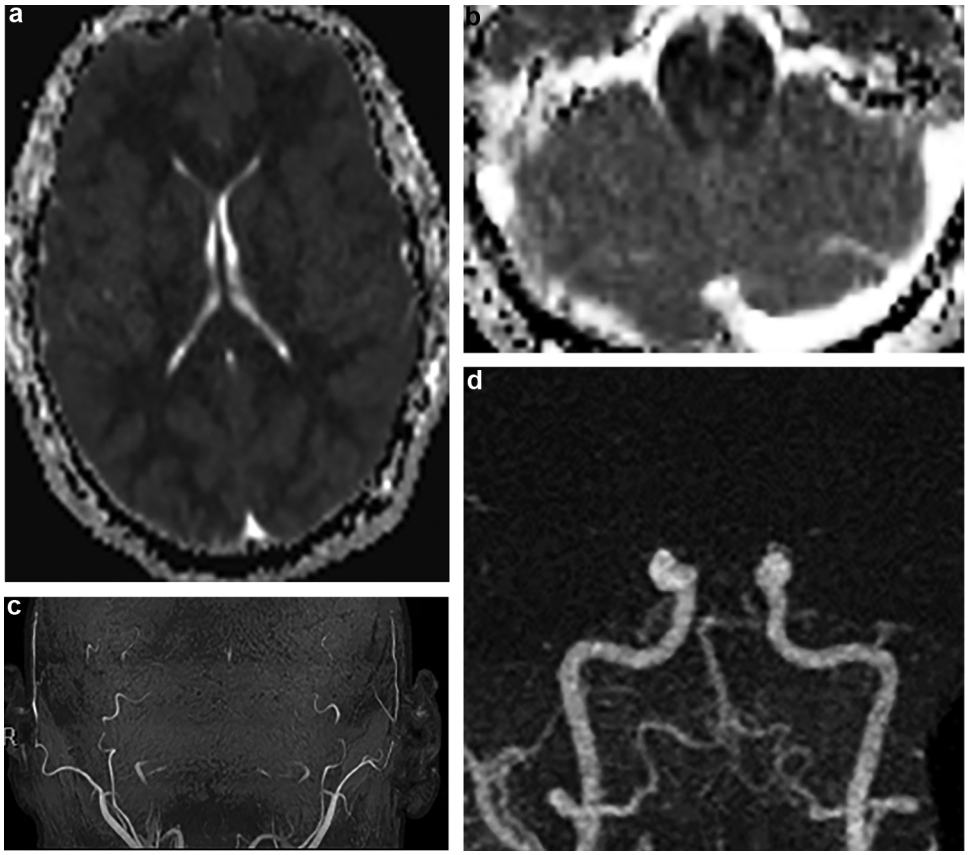

Fig. 7. 32-year-old man with brain death. Initially presented with headache, and.
CSF findings consistent with viral infection.
(a) ADC map reveals marked decreased ADC in the white matter (0.21×10^{-3} mm^2/sec) and decreased ADC in the cortex (0.51×10^{-3} mm^2/sec). Note diffuse obliteration of cortical sulci. Axial diffusion weighted image (not shown) showed diffuse increased signal intensity
(b) Decreased ADC is observed in the pons (0.30×10^{-3} mm^2/sec) but not involving the cerebellum.
(c) Intracranial time of flight MR angiography demonstrates external carotid artery branches and loss of vascular flow of internal carotid arteries.
(d) Dynamic contrast MR angiography shows loss of vascular flow within the supraclinoid internal carotid arteries but reveals opacification of intracranial vertebral and basilar arteries.

(intravascular enhancement sign), and 6) prominent nasal contrast and scalp enhancement (MR hot nose sign) [63] (Fig. 6a, b). Evidence of brain stem injury with Duret hemorrhages is also well visualized on gradient recalled echo (GRE) and susceptibility weighted imaging (SWI) (Fig. 6c). Any of these findings when in isolation, however, are not specific for brain death. For example, transtentorial and foramen magnum herniation as well as poor gray matter/white matter differentiation may also be observed in patients with severe hypoxic brain damage in the absence of brain death [64].

DWI shows diffuse decrease in the ADC values of both white and gray matter [65] (Fig. 7a). Pathologically, the decreased ADC areas specifically represent cytotoxic edema. Low ADC values are greater in white matter than gray matter for both cerebral and cerebellar hemispheres [66], which may reflect cytotoxic edema of different cellular components in the gray (neurons and glial cells) and white matter (myelin sheaths, glial cells and axons). Diffusion restriction usually extends to the brain stem and, variably, the cerebellum [66] (Figs. 6d, 7b). Extensive diffusion restriction, however, may occur in other situations, such as bilateral carotid artery occlusion [67], and this should be correlated with other findings of brain death. Another confounding factor is the difference in ADC values between MRI scanners and DWI protocols, making comparison of absolute threshold values difficult [68].

Findings on SWI and GRE include the transcerebral vein and transcortical vein signs [69] (Fig. 7d) as well as prominent medullary veins (Fig. 7d). The transcerebral vein sign refers to multiple and/or branching dark structures extending through the cerebral hemispheres parallel or perpendicular to the outer wall of both lateral ventricles; the transcortical vein sign is accentuated visualization of hemispheric cortical veins [70]. These have been described in acute stroke among other etiologies, caused by increased oxygen extraction fraction with increased deoxyhemoglobin in capillaries and veins [69,71]. Although these findings can be seen in brain death they are not specific [69].

Time of flight (TOF) MRA (Fig. 7f) and dynamic contrast enhanced MRA (Fig. 7g) have also been studied in brain death. Ishii et al. first demonstrated findings on TOF MRA, showing absence of cerebral vessels above the level of the supraclinoid ICAs, indicating cessation of blood flow[64]. The first study using gadolinium enhanced MRA by Luchtman et al. showed no intracranial contrast above the level of the anterior cerebral artery and M1 segment of the MCA, consistent with the findings on TOF MRA [72].

More recently, spin-labeling perfusion MRI has emerged as a technique for measuring cerebral blood flow. This method generates a perfusion image by subtracting signal in labeled protons in feeding arterial vasculature from background signal from unlabeled brain tissue [73]. This was found to satisfy criteria of brain death in a small series of patients (Fig. 8a, 8b) [74].

Similar to CTA, there is insufficient diagnostic confidence with MRI and MRA to be used routinely as a confirmatory test for brain death. Disadvantages include length of scanning time, lower availability, difficulty obtaining the study on a ventilated patient, and cost.

5.6. Future directions

Further research is necessary to establish validity of CTA and MRA for determination of brain death. Specifically, greater consensus is needed to establish radiographic criteria used to identify cessation of brain blood flow, including prospective assessment of lack of opacification of ICVs for the diagnosis. Other techniques, including CTP and ASL, have shown some promise, and further studies validating these techniques is needed.

Finally, resting state functional MRI is a technique that can evaluate functional neuroanatomic connectivity not possible with conventional imaging and provides a tremendous amount of additional information. This neuroanatomic connectivity has been shown to be decreased in vegetative state and brain death patients in a single-case study [75].

Although this is not as widely available as other imaging modalities, further studies with greater power may be fruitful in establishing the role of this technique in the diagnosis.

Conclusions

Brain death is caused by global irreversible brain injury. Early recognition is important to provide closure for loved ones, prevent unnecessary interventions, and support organ transplantation if applicable. Brain death remains a clinical diagnosis. However, there are circumstances in which confirmatory tests may be helpful. Imaging tests can demonstrate the absence of cerebral perfusion although the ultimate diagnosis relies on the clinical findings. Imaging in brain death continues to be performed and recognizing the imaging findings, as well as knowing the limitations of these imaging modalities, may aid in the diagnosis.

Reference:

[1] P. Mollaret, M. Goulon, The depassed coma (preliminary memoir), Rev. Neurol. (Paris) 101 (1959) 3–15.
[2] A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. JAMA. 1968; 205(6):337-40.
[3] Guidelines for the determination of death. Report of the medical consultants on the diagnosis of death to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. JAMA. 1981; 246(19):2184-6.
[4] S.J. Youngner, C.S. Landefeld, C.J. Coulton, B.W. Juknialis, M. Leary, 'Brain death' and organ retrieval. A cross-sectional survey of knowledge and concepts among health professionals, JAMA 261 (15) (1989) 2205–2210.
[5] I.M. Spinello, Brain death determination, J. Intensive Care Med. 30 (6) (2015) 326–337, https://doi.org/10.1177/0885066613511053.
[6] B. Jennett, J. Gleave, P. Wilson, Brain death in three neurosurgical units, Br. Med. J. (Clin Res Ed). 282 (6263) (1981) 533–539.
[7] H.H. Wang, P.N. Varelas, G.V. Henderson, E.F. Wijdicks, D.M. Greer, Improving uniformity in brain death determination policies over time, Neurology 88 (6) (2017) 562–568, https://doi.org/10.1212/wnl.0000000000003597.
[8] E.F. Wijdicks, P.N. Varelas, G.S. Gronseth, D.M. Greer, Evidence-based guideline update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology, Neurology 74 (23) (2010) 1911–1918, https://doi.org/10.1212/WNL.0b013e3181e242a8.
[9] E.F. Wijdicks, Determining brain death in adults, Neurology 45 (5) (1995) 1003–1011.
[10] M. Drake, A. Bernard, E. Hessel, Brain Death. Surg Clin North Am 97 (6) (2017) 1255–1273, https://doi.org/10.1016/j.suc.2017.07.001.
[11] C. Machado, Diagnosis of brain death, Neurol Int. 2 (1) (2010) e2, https://doi.org/10.4081/ni.2010.e2.
[12] S. Palmer, M.K. Bader, Brain tissue oxygenation in brain death, Neurocrit. Care. 2 (1) (2005) 17–22, https://doi.org/10.1385/ncc:2:1:017.
[13] J.E. Leestma, Neuropathology of Brain, Death, E.F. Wijdicks, Brain Death. Philadelphia: Lippincott Williams & Wilkins; (2001) 45–60.
[14] M.W. Greve, B.J. Zink, Pathophysiology of traumatic brain injury, Mt Sinai J. Med. 76 (2) (2009) 97–104, https://doi.org/10.1002/msj.20104.
[15] A. Marmarou, A review of progress in understanding the pathophysiology and treatment of brain edema, Neurosurg. Focus. 22 (5) (2007) E1.
[16] J.E. Leestma, J.R. Hughes, E.R. Diamond, Temporal correlates in brain death. EEG and clinical relationships to the respirator brain, Arch. Neurol. 41 (2) (1984) 147–152.
[17] A.H. Kramer, Ancillary testing in brain death, Semin. Neurol. 35 (2) (2015) 125–138, https://doi.org/10.1055/s-0035-1547541.
[18] A.E. Walker, Pathology of brain death, Ann. N. Y. Acad. Sci. 315 (1978) 272–280.
[19] M.K. Herrick, D.P. Agamanolis, Displacement of cerebellar tissue into spinal canal. A component of the respirator brain syndrome, Arch. Pathol. 99 (11) (1975) 565–571.
[20] M. Oehmichen, Brain death: neuropathological findings and forensic implications, Forensic Sci. Int. 69 (3) (1994) 205–219.
[21] E.F. Wijdicks, E.A. Pfeifer, Neuropathology of brain death in the modern transplant era, Neurology 70 (15) (2008) 1234–1237, https://doi.org/10.1212/01.wnl.0000289762.50376.b6.
[22] E.F. Wijdicks, The case against confirmatory tests for determining brain death in adults, Neurology 75 (1) (2010) 77–83, https://doi.org/10.1212/WNL.0b013e3181e62194.
[23] S.J. Marks, J. Zisfein, Apneic oxygenation in apnea tests for brain death. A controlled trial, Arch. Neurol. 47 (10) (1990) 1066–1068.
[24] M. Mathur, S. Ashwal, Pediatric brain death determination, Semin. Neurol. 35 (2) (2015) 116–124, https://doi.org/10.1055/s-0035-1547540.
[25] M.K. Heran, N.S. Heran, S.D. Shemie, A review of ancillary tests in evaluating brain death, Can. J. Neurol. Sci. 35 (4) (2008) 409–419.
[26] G. Valle, P. Ciritella, M.G. Bonetti, F. Dicembrino, E. Perrone, G.P. Perna, Considerations of brain death on a SPECT cerebral perfusion study, Clin. Nucl. Med. 18 (11) (1993) 953–954.
[27] G. Citerio, I.A. Crippa, A. Bronco, A. Vargiolu, M. Smith, Variability in brain death determination in europe: looking for a solution, Neurocrit. Care. 21 (3) (2014) 376–382, https://doi.org/10.1007/s12028-014-9983-x.
[28] C.N. Shappell, J.I. Frank, K. Husari, M. Sanchez, F. Goldenberg, A. Ardelt, Practice variability in brain death determination: a call to action, Neurology. 81 (23) (2013) 2009–2014, https://doi.org/10.1212/01.wnl.0000436938.70528.4a.
[29] D.M. Greer, H.H. Wang, J.D. Robinson, P.N. Varelas, G.V. Henderson, E.F. Wijdicks, Variability of Brain Death Policies in the United States, JAMA Neurol. 73 (2) (2016) 213–218, https://doi.org/10.1001/jamaneurol.2015.3943.
[30] A. Pandey, P. Sahota, P. Nattanmai, C.R. Newey, Variability in Diagnosing Brain Death at an Academic Medical Center, Neurosci. J. 2017 (2017) 6017958, https://doi.org/10.1155/2017/6017958.
[31] E.F. Wijdicks, Brain death worldwide: accepted fact but no global consensus in diagnostic criteria, Neurology 58 (1) (2002) 20–25.
[32] G.B. Bradac, R.S. Simon, Angiography in brain death, Neuroradiology 7 (1) (1974) 25–28.
[33] T.W. Langfitt, N.F. Kassell, Non-filling of cerebral vessels during angiography: correlation with intracranial pressure, Acta Neurochir. (Wien). 14 (1) (1966) 96–104.
[34] Practice parameters for determining brain death in adults (summary statement). The Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 1995; 45(5):1012-4.
[35] M. Braum, X. Ducrocq, J.C. Huot, G. Audibert, R. Anxionnat, L. Picard, Intravenous angiography in brain death: report of 140 patients, Neuroradiology 39 (6) (1997) 400–405.
[36] W.M. Flowers Jr., B.R. Patel, Persistence of cerebral blood flow after brain death, South Med. J. 93 (4) (2000) 364–370.
[37] X. Ducrocq, W. Hassler, K. Moritake, D.W. Newell, G.M. von Reutern, T. Shiogai, et al., Consensus opinion on diagnosis of cerebral circulatory arrest using Doppler-sonography: Task Force Group on cerebral death of the Neurosonology Research Group of the World Federation of Neurology, J. Neurol. Sci. 159 (2) (1998) 145–150.
[38] J.J. Chang, G. Tsivgoulis, A.H. Katsanos, M.D. Malkoff, A.V. Alexandrov, Diagnostic Accuracy of Transcranial Doppler for Brain Death Confirmation: Systematic Review and Meta-Analysis, AJNR Am. J. Neuroradiol. 37 (3) (2016) 408–414, https://doi.org/10.3174/ajnr.A4548.
[39] M. Hadani, B. Bruk, Z. Ram, N. Knoller, R. Spiegelmann, E. Segal, Application of transcranial doppler ultrasonography for the diagnosis of brain death, Intensive Care Med. 25 (8) (1999) 822–828.
[40] W. Hassler, H. Steinmetz, J. Pirschel, Transcranial Doppler study of intracranial circulatory arrest, J. Neurosurg. 71 (2) (1989) 195–201, https://doi.org/10.3171/jns.1989.71.2.0195.
[41] G.B. Young, S.D. Shemie, C.J. Doig, J. Teitelbaum, Brief review: the role of ancillary tests in the neurological determination of death, Can. J. Anaesth. 53 (6) (2006) 620–627, https://doi.org/10.1007/bf03021855.
[42] K.J. Donohoe, G. Agrawal, K.A. Frey, V.H. Gerbaudo, G. Mariani, J.S. Nagel, et al., SNM practice guideline for brain death scintigraphy 2.0, J. Nucl. Med. Technol. 40 (3) (2012) 198–203, https://doi.org/10.2967/jnmt.112.105130.
[43] G.R. Conrad, P. Sinha, Scintigraphy as a confirmatory test of brain death, Semin. Nucl. Med. 33 (4) (2003) 312–323.
[44] D.S. Schauwecker, Tc-99m HMPAO brain survival study reveals flow to the cerebrum but none to the cerebellum, Clin. Nucl. Med. 17 (12) (1992) 984–985.
[45] F.S. Mishkin, M.L. Dyken, Increased early radionuclide activity in the nasopharyngeal area in patients with internal carotid artery obstruction: "hot nose", Radiology 96 (1) (1970) 77–80, https://doi.org/10.1148/96.1.77.
[46] F. Mishkin, Determination of cerebral death by radionuclide angiography, Radiology 115 (1) (1975) 135–137, https://doi.org/10.1148/115.1.135.
[47] A.R. Joffe, L. Lequier, D. Cave, Specificity of radionuclide brain blood flow testing in brain death: case report and review, J. Intensive Care Med. 25 (1) (2010) 53–64, https://doi.org/10.1177/0885066609355388.
[48] E.F. Wijdicks, The diagnosis of brain death, N. Engl. J. Med. 344 (16) (2001) 1215–1221, https://doi.org/10.1056/nejm200104193441606.
[49] A. van der Lugt, Imaging tests in determination of brain death, Neuroradiology 52 (11) (2010) 945–947, https://doi.org/10.1007/s00234-010-0765-7.
[50] B. Dupas, M. Gayet-Delacroix, D. Villers, D. Antonioli, M.F. Veccherini, J.P. Soulillou, Diagnosis of brain death using two-phase spiral CT, AJNR Am. J. Neuroradiol. 19 (4) (1998) 641–647.
[51] J.C. Combes, A. Chomel, F. Ricolfi, P. d'Athis, M. Freysz, Reliability of computed tomographic angiography in the diagnosis of brain death, Transpl. Proc. 39 (1) (2007) 16–20, https://doi.org/10.1016/j.transproceed.2006.10.204.
[52] X. Leclerc, C.A. Taschner, A. Vidal, G. Strecker, J. Savage, J.Y. Gauvrit, et al., The role of spiral CT for the assessment of the intracranial circulation in suspected brain-death, J. Neuroradiol. 33 (2) (2006) 90–95.
[53] C. Quesnel, J.P. Fulgencio, C. Adrie, B. Marro, L. Payen, N. Lembert, et al., Limitations of computed tomographic angiography in the diagnosis of brain death, Intensive Care Med. 33 (12) (2007) 2129–2135, https://doi.org/10.1007/s00134-007-0789-6.
[54] E. Frampas, M. Videcoq, E. de Kerviler, F. Ricolfi, V. Kuoch, F. Mourey, et al., CT angiography for brain death diagnosis, AJNR Am. J. Neuroradiol. 30 (8) (2009) 1566–1570, https://doi.org/10.3174/ajnr.A1614.
[55] M. Sawicki, R. Bohatyrewicz, K. Safranow, A. Walecka, J. Walecki, O. Rowinski, et al., Computed tomographic angiography criteria in the diagnosis of brain death-comparison of sensitivity and interobserver reliability of different evaluation scales, Neuroradiology 56 (8) (2014) 609–620, https://doi.org/10.1007/s00234-014-

1364-9.
[56] T. Taylor, R.A. Dineen, D.C. Gardiner, C.H. Buss, A. Howatson, N.L. Pace, Computed tomography (CT) angiography for confirmation of the clinical diagnosis of brain death, Cochrane Database Syst. Rev. 3 (2014) CD009694, https://doi.org/10.1002/14651858.CD009694.pub2.
[57] J.J. Shankar, R. Vandorpe, CT perfusion for confirmation of brain death, AJNR Am. J. Neuroradiol. 34 (6) (2013) 1175–1179, https://doi.org/10.3174/ajnr.A3376.
[58] D. Escudero, J. Otero, L. Marques, D. Parra, J.A. Gonzalo, G.M. Albaiceta, et al., Diagnosing brain death by CT perfusion and multislice CT angiography, Neurocrit. Care. 11 (2) (2009) 261–271, https://doi.org/10.1007/s12028-009-9243-7.
[59] A.H. Kramer, D.J. Roberts, Computed tomography angiography in the diagnosis of brain death: a systematic review and meta-analysis, Neurocrit. Care 21 (3) (2014) 539–550, https://doi.org/10.1007/s12028-014-9997-4.
[60] S. Brasil, E. Bor-Seng-Shu, M. de-Lima-Oliveira, J.T. Bernardo, et al., Role of computed tomography angiography and perfusion tomography in diagnosing brain death: A systematic review, J. Neuroradiol. 43 (2) (2016) 133–140, https://doi.org/10.1016/j.neurad.2015.07.006.
[61] M.P. Garrett, R.W. Williamson, M.A. Bohl, C.R. Bird, N. Theodore, Computed tomography angiography as a confirmatory test for the diagnosis of brain death, J. Neurosurg. 128 (2) (2018) 639–644, https://doi.org/10.3171/2016.10.Jns161042.
[62] S. Welschehold, T. Kerz, S. Boor, K. Reuland, F. Thomke, A. Reuland, et al., Computed tomographic angiography as a useful adjunct in the diagnosis of brain death, J. Trauma Acute Care Surg. 74 (5) (2013) 1279–1285, https://doi.org/10.1097/TA.0b013e31828c46ba.
[63] W.W. Orrison Jr., A.M. Champlin, O.L. Kesterson, M.F. Hartshorne, J.N. King, MR 'hot nose sign' and 'intravascular enhancement sign' in brain death, AJNR Am. J. Neuroradiol. 15 (5) (1994) 913–916.
[64] K. Ishii, T. Onuma, T. Kinoshita, G. Shiina, M. Kameyama, Y. Shimosegawa, Brain death: MR and MR angiography, AJNR Am. J. Neuroradiol. 17 (4) (1996) 731–735.
[65] K. Kumada, A. Fukuda, K. Yamane, I. Horiuchi, A. Kohama, K. Hirano, et al., [Diffusion-weighted imaging of brain death: study of apparent diffusion coefficient], No To Shinkei. 53 (11) (2001) 1027–1031.
[66] H. Selcuk, S. Albayram, E. Tureci, Z.I. Hasiloglu, O. Kizilkilic, E. Cagil, et al., Diffusion-weighted imaging findings in brain death, Neuroradiology 54 (6) (2012) 547–554, https://doi.org/10.1007/s00234-011-0912-9.
[67] T.G. Phan, E.F. Wijdicks, Diffusion-weighted magnetic resonance imaging in brain death, Stroke. 31 (6) (2000) 9–60 1458-9; author reply.
[68] M. Luchtmann, J. Bernarding, O. Beuing, J. Kohl, I. Bondar, M. Skalej, et al., Controversies of diffusion weighted imaging in the diagnosis of brain death, J. Neuroimaging. 23 (4) (2013) 463–468, https://doi.org/10.1111/jon.12033.
[69] C.-H. Sohn, L. Hwa-Pyung, J.B. Park, H.W. Chang, E. Kim, E. Kim, et al., Imaging Findings of Brain Death on 3-Tesla MRI, KJR 13 (5) (2012) 541–549.
[70] N. Morita, M. Harada, M. Uno, S. Matsubara, T. Matsuda, S. Nagahiro, et al., Ischemic findings of T2*-weighted 3-tesla MRI in acute stroke patients, Cerebrovasc. Dis. 26 (4) (2008) 367–375, https://doi.org/10.1159/000151640.
[71] K.A. Tong, S. Ashwal, A. Obenaus, J.P. Nickerson, D. Kido, E.M. Haacke, Susceptibility-weighted MR imaging: a review of clinical applications in children, AJNR Am. J. Neuroradiol. 29 (1) (2008) 9–17, https://doi.org/10.3174/ajnr.A0786.
[72] M. Luchtmann, O. Beuing, M. Skalej, J. Kohl, S. Serowy, J. Bernarding, et al., Gadolinium-enhanced magnetic resonance angiography in brain death, Sci. Rep. 4 (2014) 3659, https://doi.org/10.1038/srep03659.
[73] T.J. Yun, C.H. Sohn, B.W. Yoon, B.S. Jeon, S.H. Choi, J.H. Kim, et al., Brain death: evaluation of cerebral blood flow by use of arterial spin labeling, Circulation. 124 (23) (2011) 2572–2573, https://doi.org/10.1161/circulationaha.111.060574.
[74] K.M. Kang, T.J. Yun, B.W. Yoon, B.S. Jeon, S.H. Choi, J.H. Kim, et al., Clinical utility of arterial spin-labeling as a confirmatory test for suspected brain death, AJNR Am. J. Neuroradiol. 36 (5) (2015) 909–914, https://doi.org/10.3174/ajnr.A4209.
[75] M. Boly, L. Tshibanda, A. Vanhaudenhuyse, Q. Noirhomme, C. Schnakers, D. Ledoux, et al., Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient, Hum. Brain Mapp. 30 (8) (2009) 2393–2400, https://doi.org/10.1002/hbm.20672.
[76] A. Matsumura, K. Meguro, H. Tsurushima, Y. Komatsu, Y. Kikuchi, M. Wada, et al., Magnetic resonance imaging of brain death, Neurol. Med. Chir. (Tokyo). 36 (3) (1996) 166–171, https://doi.org/10.2176/nmc.36.166.
[77] A.H. Karantanas, G.M. Hadjigeorgiou, K. Paterakis, D. Sfiras, A. Komnos, Contribution of MRI and MR angiography in early diagnosis of brain death, Eur. Radiol. 12 (11) (2002) 2710–2716, https://doi.org/10.1007/s00330-002-1336-z.
[78] M. Sawicki, J. Solek-Pastuszka, K. Jurczyk, P. Skrzywanek, M. Guzinski, Z. Czajkowski, et al., Original Protocol Using Computed Tomographic Angiography for Diagnosis of Brain Death: A Better Alternative to Standard Two-Phase Technique? Ann. Transplant. 20 (2015) 449–460, https://doi.org/10.12659/aot.893808.
[79] H. Sahin, Y. Pekcevik, CT angiography as a confirmatory test in diagnosis of brain death: comparison between three scoring systems, Diagn. Interven. Radiol. (Ankara, Turkey). 21 (2) (2015) 177–183, https://doi.org/10.5152/dir.2014.14241.