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OPINION

How should we use imaging in the determination of brainstem death?

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ABSTRACT

Brainstem death is defined as the "irreversible cessation of brainstem function", either due to primary intracranial events or extracranial factors such as hypoxia. The importance of accurate and timely diagnosis of brainstem death in critical care should not be understated, as it allows the withdrawal of treatment when it is no longer deemed to beneficial. Additionally, it may facilitate the process of organ donation. Overall, the diagnosis of brainstem death has four common principles across the world: (1) neurological criteria based on clinical assessment; (2) evidence of irreversible brain damage from known aetiology; (3) demonstrating an absence of a reversible cause; and (4) the use of ancillary studies. The latter in particular has been a controversial issue, with much debate continuing on how imaging should be used. We discuss three key questions surrounding the role of imaging in the diagnosis of brainstem death as well as important issues the radiology community should consider.

Firstly, we ask the question whether imaging should be used at all. Since the start of the century, there has been significant variation internationally in the use of ancillary studies.[1] While many countries recommend imaging only in certain circumstances, it is legally required in some as an essential part of diagnosing brainstem death. Indeed, such ongoing variation in practice has been demonstrated in Europe.[2] Furthermore, studies have demonstrated variation even within countries[3] and deviation from national guidelines.[4] The cause of this variation is complex and multifactorial, but is likely to include medicolegal, religious and cultural issues, in addition to unclear evidence, individual physician biases and differing organ donation processes. There are particular circumstances in which imaging is invaluable, such as when: (a) neurological assessment cannot be performed (*e.g.* due to severe maxillofacial injuries); (b) a primary metabolic or pharmacological phenomenon cannot be excluded as an aetiology; (c) there is high cervical cord injury; and (d) there is diagnostic uncertainty due to spontaneous or reflex movements.[5] In situations where these do not apply, however, the decision to employ imaging as a confirmatory or screening method becomes less clear. The initial use of standard non-contrast CT is less disputed as it can simultaneously provide evidence for both irreversible brain damage and a primary intracranial event as a precipitant. Cases of false-positives (*i.e.* where imaging suggests brainstem death but the patient does not meet clinical criteria) with other modalities remind us that imaging may create legal and clinical challenges.[6] Conversely, false-negatives may lead to further confirmatory investigations with no guarantee of resolution, be a potential source of distress for families and may increase opposition to organ donation. It has been further argued that the presence of significant areas of viable brain tissue from pathology studies in patients deemed clinically brainstem dead reduces the diagnostic utility of some imaging as confirmatory tests.[7] Moreover, factors such as cost, availability of the imaging modality and stability of the patient for transfer are key issues to consider. For all these reasons, case-by-case discussions between the intensive care physician and radiologist are still essential in formulating decisions to perform imaging, regardless of guideline recommendations. The radiology community can play a significant role in collaborating with intensive care physicians to reach an international consensus and to outline research priorities to establish an acceptable evidence base.

Secondly, we discuss which imaging modality should be recommended. This question is intrinsically linked to the first as the availability of a valid and reliable

imaging modality is an important pre-requisite in the decision to perform imaging. The literature describes six methods to assist in the diagnosis of brainstem death: four vessel catheter angiography, CT angiography (CTA), radionuclide studies including single-photon emission CT (SPECT), CT perfusion (CTP), transcranial ultrasound Doppler (TCD) and MRI. We summarise the current evidence and key considerations for each modality below:

- *Four vessel intra arterial catheter angiography:* For over three decades, catheter angiography has generally been deemed the gold-standard[8] as it allows direct visualisation and evaluation of intra-arterial collapse. Its use is limited by its invasiveness and time and expertise required to perform the procedure.
- *CTA*: Two systematic reviews have demonstrated inadequate evidence to support the use of CTA, due in part to a small combined sample sizes.[9,10] While CTA appears to have high sensitivity in confirming brainstem death, its performance as a screening tool is unclear.[9] As with some of the modalities below, there have been no large studies with matched controls.
- *Radionuclide studies*: Radionuclide studies have the theoretical advantage of measuring both cerebral metabolism and blood flow in the brainstem. There is a small but growing evidence base for radionuclide studies. A review of the literature up to 2008 has demonstrated a pooled sensitivity (88.4%) and specificity (100%) for confirming brainstem death, albeit with small sample sizes.[11] SPECT has also been shown to compare favourably with CTA.[12] It has been recommended that both anterior and lateral views be used to improve reliability.[11] The main disadvantage is that only radiopharmaceuticals that can cross the blood–brain barrier can be used, such as 99mTc-hexamethylpropyleneamineoxime (*99mTc-HMPAO*), which may create sourcing issues in some institutions.
- *CTP*: The advantage of CTP is that it provides a functional assessment of the brainstem. A handful of prospective studies have evaluated CTP and suggest strong reliability.[13,14] One study suggests that the sensitivity of CTA can be boosted by concurrent use of CTP.[13]
- *TCD*: A recent meta-analysis showed promising accuracy for TCD with a pooled sensitivity and specificity of 90 and 98% respectively.[15] The main drawbacks of TCD are that it assesses circulatory flow as opposed to brainstem function and is operator dependent. Its sensitivity may also be reduced in patients with large cranial defects, skull fractures or cerebrospinal fluid drainage.[16] TCD represents a potential useful screening tool to optimise timing of contrast studies by demonstrating cessation of blood flow.
- *MRI*: A few small scale studies have demonstrated potential utility with MR angiography and MRI, including Class II evidence involving matched controls (*i.e.* comatose patients with no clinical evidence of brainstem death).[17] MRI may reveal parenchymal changes consistent with brainstem death, including tonsillar herniation and widespread high signal on diffusion-weighted imaging with corresponding reduction in the apparent diffusion coefficient. There are a number of technical parameters which may influence the sensitivity of MRI including field strength, sequence type and slice thickness. Indeed, certain techniques may create false-positives due to insufficient sensitivity to slow flow. Transferring critically ill patients to MRI may also pose a greater logistical challenge compared to other modalities.

There is currently wide variation in which modalities have been recommended. For example, while the UK guidelines do not openly favour one modality over another,[5] the Australia and New Zealand Intensive Care Society specifically recommends four vessel catheter angiography and radionuclide studies, but not MRI or TCD.[8] An international set of guidelines will need to reflect issues such as the cost-effectiveness and availability of the appropriate modality (*e.g.* sourcing radiopharmaceuticals for radionuclide studies), particularly for resource-constrained settings.

Thirdly, we consider the timing of imaging. For this, the radiologist needs to have an understanding of the physiological processes leading to brainstem death. It has been suggested that the vast majority of cases of brainstem death are a result of catastrophic supratentorial pathology, with only around 2% being due to isolated brainstem lesions.[18] The most likely mechanism starts with cerebral oedema, which would lead to the posterior cerebro spinal fluid pathways being impeded. There would be subsequent development of obstructive hydrocephalus which would cause an increase in the intracranial pressure. This in turn will eventually reduce the cerebral perfusion pressure to zero, resulting in collapse of intracranial blood flow. It follows that the process of brainstem death in the context of supratentorial pathology is a process rather than a single event. Consequently, only a snapshot may be provided in imaging that examines circulatory status. This should be borne in mind when interpreting such studies, as persistence in blood flow at one stage may lead to cessation at a later stage. Furthermore, this may reduce clinicians' confidence in diagnosing brainstem death and leads to the question whether repeat or serial imaging should be performed to confirm ultimate circulatory collapse. As discussed earlier, the use of TCD may prevent premature contrast-based imaging (*i.e.* before cessation of blood flow has been established).

To conclude, there still remains significant controversy in the role of imaging in diagnosing brainstem death. The need for a unified global consensus and formulation of a research agenda in how imaging should be used is ever growing. The radiology community has the opportunity to work in collaboration with intensive care physicians to facilitate this process. Given that at present there is no ideal imaging modality, it is unlikely that imaging will universally form a compulsory part of diagnosing brainstem death in the near future. Nevertheless, imaging currently has important applications in supporting a diagnosis and is invaluable in certain clinical situations. Finally, radiologists should be mindful of the underlying physiological processes in brainstem death when interpreting certain studies.

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