

Radionuclide Evaluation of Brain Death in the Post-McMath Era, epilogue and enigmata.

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INTRODUCTION

On occasion a patient's medical odyssey emerges from obscurity into the public domain. Jahi McMath was an unfortunate 13-year-old girl who suffered a cardiac arrest following surgery and was subsequently declared dead by neurologic criteria (hereafter referred to as "brain dead", abbreviated "BD"). Her family successfully petitioned the courts to prevent interruption of supportive care. She was maintained on a ventilator for 4.5 years until suffering cardiopulmonary arrest in June 2018.

Because the profound and protracted legal arguments surrounding Jahi's medical course resulted in extensive media coverage, many clinical details were disclosed in the public domain, which served as a nidus for editorials and reviews in the medical literature. An article on radionuclide evaluation of BD appeared in this journal in 2016, reviewing the initial course of Jahi McMath's illness and discussing the role of scintigraphy in the determination of BD (1). Jahi's entire medical records were released, including images from a radionuclide BD examination (2). This editorial will update the prior report by providing additional clinical history, radionuclide images and their analysis, and a discussion of controversy and questions engendered by this tragic case. Clinical information presented herein is in the public domain, either in previously published literature, or with permission granted by Jahi's mother.

CHRONOLOGY

In 2013, Jahi McMath presented with symptoms of obstructive sleep apnea and underwent surgery to resect offending tonsillar tissues (chronology in supplemental table 1). In the post-operative period, she bled into her airway, suffered a cardiac arrest, was resuscitated, and then placed on a ventilator. On postoperative day 3, hospital physicians determined that she met the clinical criteria for BD (3); however, the family insisted that supportive therapy be maintained. Electroencephalogram studies at that time were isoelectric. On day 14, a ^{99m}Tc-bicisate study

was performed which supported the diagnosis of BD (described in the following section) and a court-appointed pediatric neurologist meticulously repeated the clinical determination of BD, independently confirming the diagnosis. By legal means, the family compelled the hospital to maintain life support until Jahi was released to her mother on day 27. She was then moved to New Jersey where an exemption to BD can be invoked to accommodate personal religious beliefs, initially to a medical facility and subsequently to a private apartment. She remained on a ventilator until experiencing cardiovascular collapse 4.5 years after the initial BD pronouncement.

SCINTIGRAPHIC IMAGING AND FINDINGS

According to guidelines, ancillary studies are not required to establish the diagnosis of BD unless certain elements of the physical examination cannot be properly performed. They may still have a role to play for social reasons, such as allowing family members to better comprehend the diagnosis (3), which most aptly fits the current circumstance. Brain scintigraphy with lipophilic compounds may also play a separate role in prognosticating potential recovery in patients with catastrophic brain injury, even when not directly related to BD determination, which may be helpful to family and caregivers in decision making.

On day 14 of Jahi's course, a perfusion study of the brain was performed following injection of 1.0 GBq of ^{99m}Tc-bicisate (Neurolite). Twenty scintigraphic imaging files were provided on an eFilm Lite disk (Version 4.1.0, Merge Healthcare, Hartland, WI); these were provided without any editorial stipulations. Representative images are displayed in figures 1-3; additional images are presented in supplemental figures 1-4. Tomographic information was provided as secondary-capture images, not amenable to scrolling or to triangulation between planes, and lacking the original dynamic range of counts (though the windowing appears grossly adequate). These limitations should not be regarded as consequential because according to guidelines, tomographic imaging is an optional component of BD studies. The examination was

otherwise technically adequate, with performance closely conforming to published guidelines (4,5). No intracranial blood flow or parenchymal perfusion was visualized on dynamic, static, or tomographic phases of the examination.

CONTROVERSY REGARDING THE MEDICAL COURSE

While inconsistency in BD determination has been documented in the literature and potentially could lead to a false-positive diagnosis, it is unlikely that both of Jahi's clinical examinations were invalid because of the enhanced expertise focused on her high-profile case. Her perfusion study was fully compliant with relevant guidelines and no intracranial blood flow or parenchymal brain uptake were apparent.

Physicians involved in performing radionuclide BD studies should be aware of wide-ranging discussions in the clinical literature regarding Jahi McMath's case (2,6). Initial conceptualization of BD frequently included rationalization that lack of central control and coordination precluded continued integration of the organism. Although this dogma was largely abandoned, it is still distinctly unusual for a BD patient to maintain homeostasis over a span of several years, regulate body temperature, develop signs of puberty, and experience several menstrual cycles, as Jahi did. Jahi's course was also exceptional in that most patients declared BD immediately proceed to organ donation or are removed from the ventilator leaving no opportunity for subsequent observation; under these circumstances, the frequency of delayed return of function cannot be estimated. In spite of this paradigm, occasional case reports have surfaced where neurologic function is noted to return following pronouncement of BD (7), similar to our narrative. Several medical personnel, including a prominent pediatric neurologist, came to believe that Jahi could intermittently respond in a purposeful manner to verbal commands (such as "move your arm") (2). Additionally, the MRI examination performed 10 months following initial cardiac arrest unexpectedly demonstrated large regions of grossly intact brain including cortex, basal ganglia, thalamus, upper brainstem, and cerebellum, which could serve as a structural

basis for intermittent consciousness (8). Return of minimal responsiveness, if present, would directly challenge the presumption that BD is definitive and permanent.

DISCUSSION

Along with broader concerns raised by Jahi McMath's case, it is also opportune to consider several questions pertaining to nuclear medicine. Thresholds of minimal detectable perfusion have never been determined for scintigraphic studies using either lipophobic or lipophilic radiopharmaceuticals, though these parameters are basic to their interpretation. For lipophobic radiopharmaceuticals, marginal perfusion would certainly be difficult to appreciate on noisy 1- or 2-second dynamic images. For lipophilic compounds, the brainstem and small cortical regions adjacent to the calvarium represent areas where identification of minimal perfusion would be challenging, even with tomography. Coupled with uncertainty regarding the amount of blood flow required to maintain structural integrity and function of neurologic tissue, it is difficult to assert that absent visualization of blood flow on a scintigraphic study would predict complete necrosis of the brain or even guarantee absence of function. This concern seems realized in Jahi's case where perfusion was not visible on the ^{99m}Tc -bicisate study yet large regions of cerebral cortex remained intact, and according to some experts, a minimally conscious state emerged. Previous analysis of PET perfusion data in adults has suggested that the minimal regional cerebral blood flow necessary for preservation of tissue integrity is ≥ 15 ml/(100 g-min), while that required for normal neurological function is ≥ 19 ml/(100 g-min) (9). Could this amount of perfusion have been present but not visible on the ^{99m}Tc -bicisate study? Conversely, was perfusion absent during scintigraphy, possibly due to a transient hypotensive episode, but subsequently returned? Our fundamental lack of knowledge regarding behavior of the ^{99m}Tc -bicisate examination prevents us from arriving at definitive answers.

A related issue concerns estimating specificity of scintigraphy for determination of BD. Characterization of specificity requires evaluation of the examination in a population of subjects

similar to that possessing the condition in question but lacking the particular condition itself. The ancillary examination must therefore be studied in a cohort of patients with catastrophic brain injury but without complete loss of function. This has not occurred for many of the modalities, because this group of patients is simply not sent for ancillary study; if the clinical examination reveals any residual neurological function the blood flow study is deferred. This fundamental limitation has compromised validation studies in the nuclear medicine literature which have included only a handful of appropriately non-brain-dead subjects. In one study utilizing lipophobic methods, 10 appropriate non-BD patients were enrolled, but specificity for determining BD was a paltry 50% (10). Presumably lipophilic radiopharmaceuticals would possess higher specificity, but this has not been rigorously demonstrated.

CONCLUSION

Jahi McMath's tragic narrative highlights several unanswered questions relevant to the diagnosis of BD. For several decades, radionuclide techniques have served an important ancillary role in complementing incomplete clinical BD examinations though they remain incompletely characterized. Radionuclide BD examinations are invaluable when they demonstrate unexpected intracranial blood flow, preventing erroneous determination of BD; inferences when blood flow is not visualized remain more enigmatic. The threshold of blood flow required for visualization remains unknown. The accepted role of an ancillary test is to supplement but never replace the physical BD examination, which is congruent with an imperfect specificity of these ancillary tests. For this reason, SNMMI guidelines appropriately recommend that the impression of a positive study conclude "shows no evidence of brain perfusion" rather than "demonstrates BD" (4). The subjective formulation "shows no evidence" is also particularly appropriate in that it avoids the fundamentally unsubstantiated claim that "no blood flow is present". A more thorough and robust understanding of these tests, combined with an

effort to standardize their implementation, could serve to bolster their role in the determination of BD, especially in difficult or controversial circumstances.

DISCLOSURE

No potential conflicts of interest relevant to this article exist.

ACKNOWLEDGMENT

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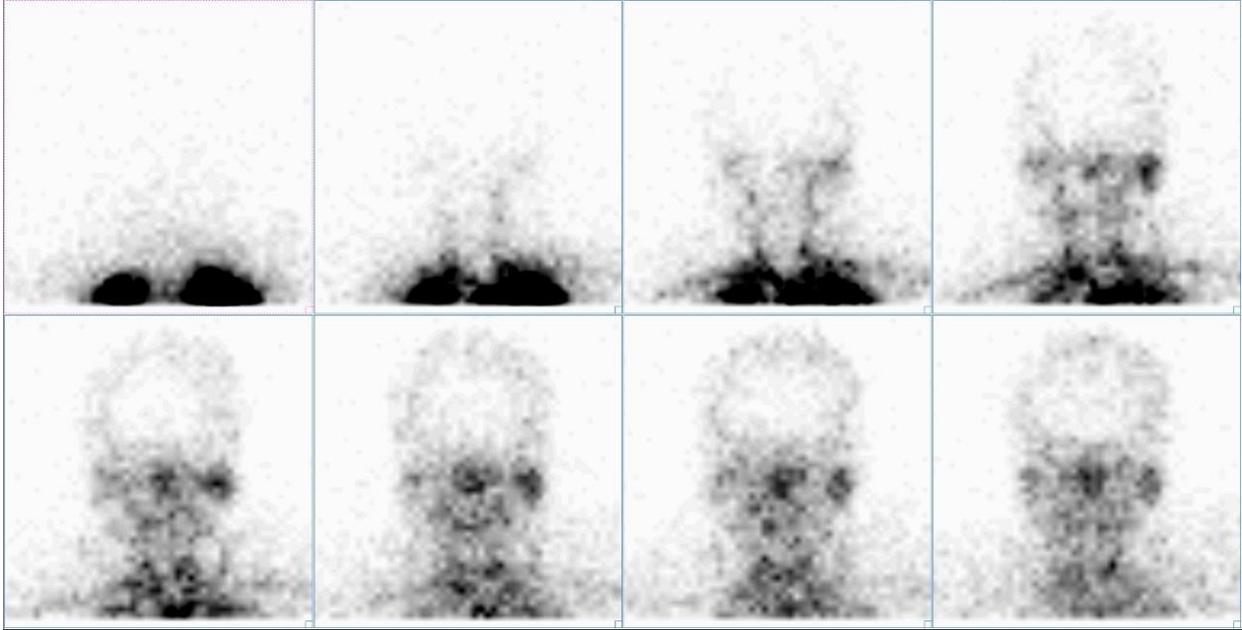


Figure 1. 1.0 GBq of ^{99m}Tc -bicisate was injected via femoral central line with scalp tourniquet in place. Representative dynamic images were selected from the series of 95 rapid sequential images acquired in anterior projection at 1- or 2-second intervals (timing details not specified in the images or report). Activity is clearly seen within the common carotid arteries; however, no intracranial flow is visualized.

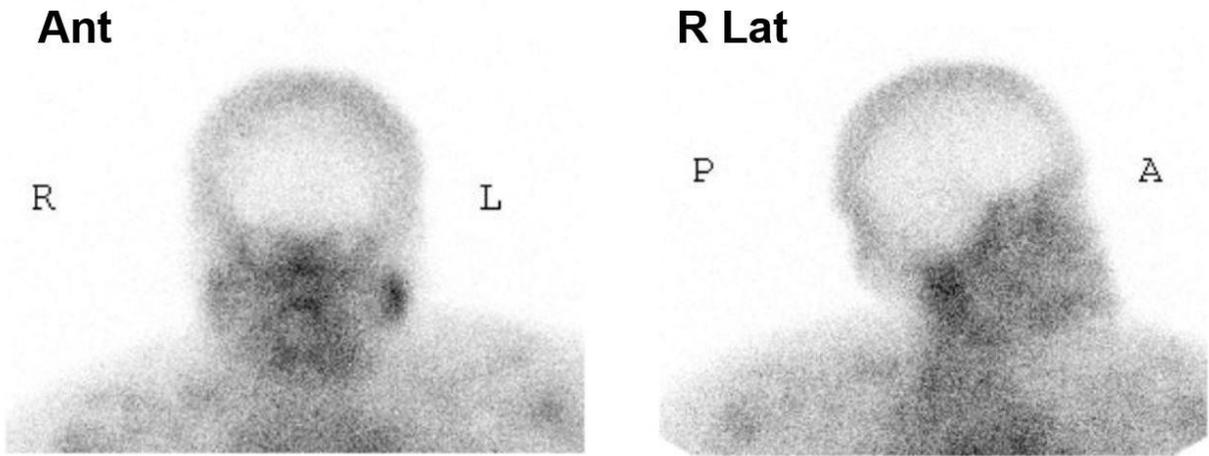


Figure 2. Anterior and right lateral views imaged several minutes following injection demonstrate activity in the extracranial tissues of the face and skull. No activity is localized in the cerebrum or cerebellum.

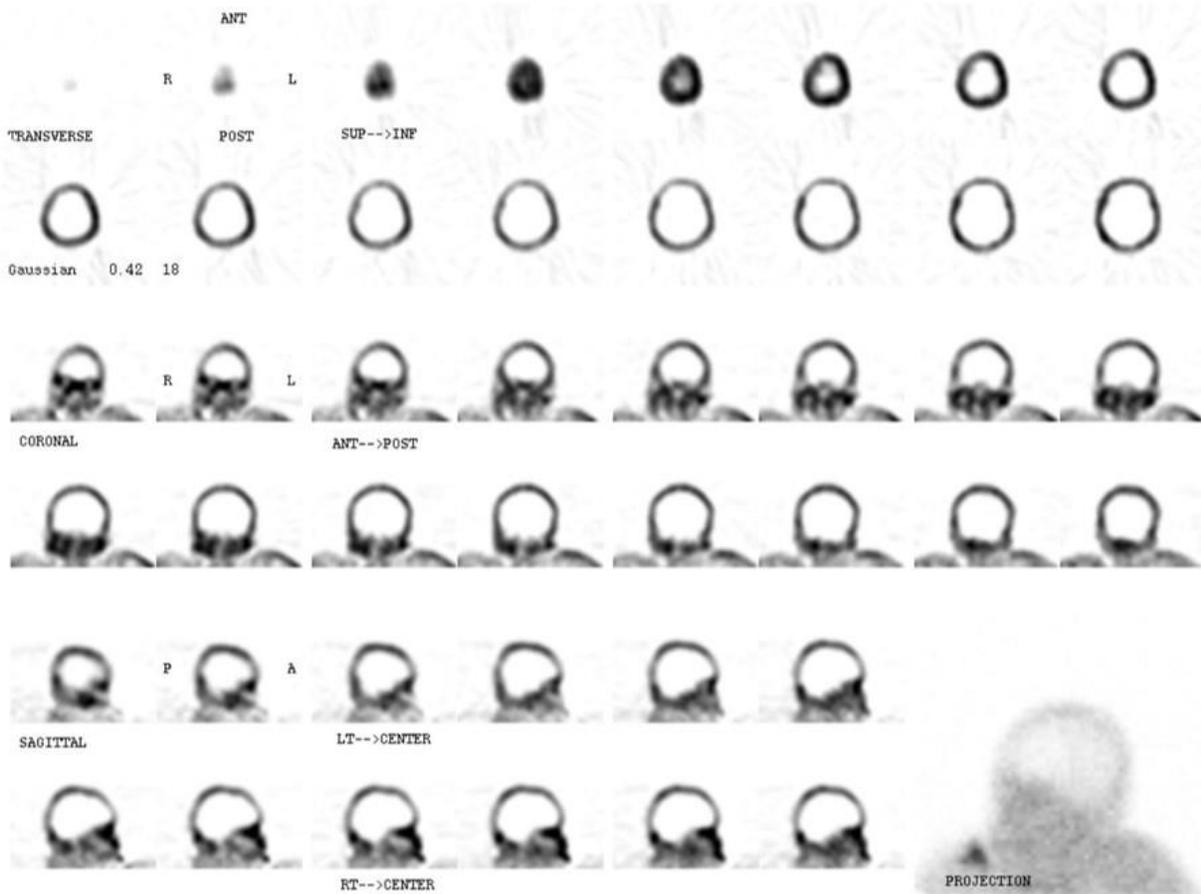


Figure 3. Representative tomographic images, displayed in transaxial, coronal and sagittal planes. No activity is visualized within the calvarium. Additional images appear in the supplemental figures.

SUPPLEMENTAL FIGURES

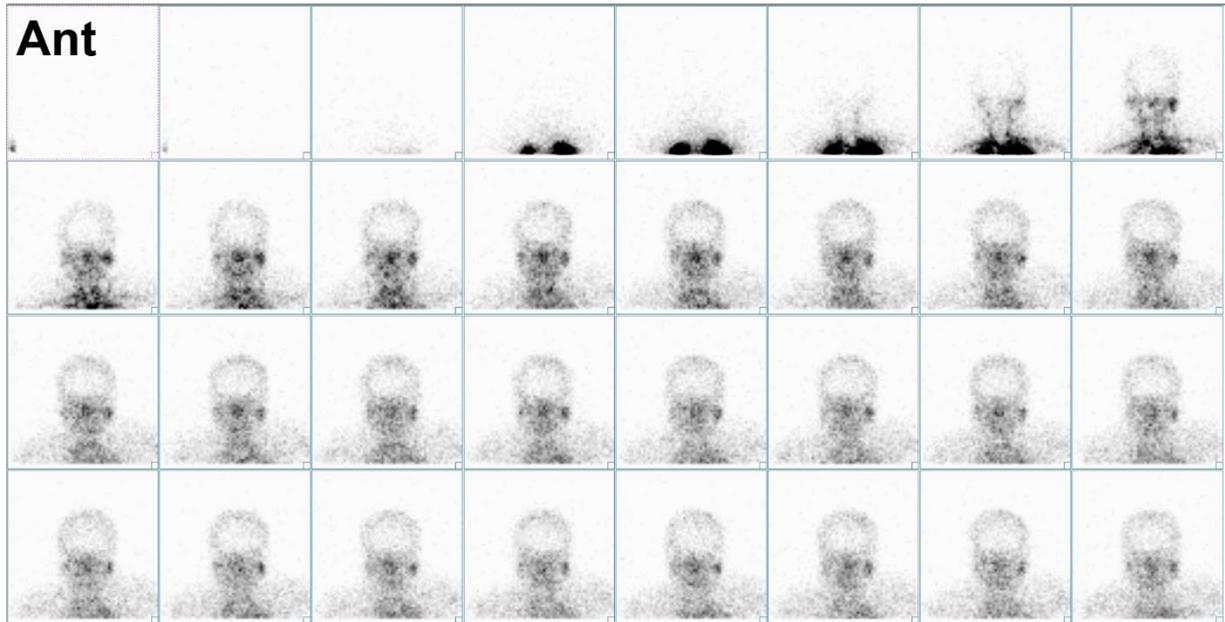
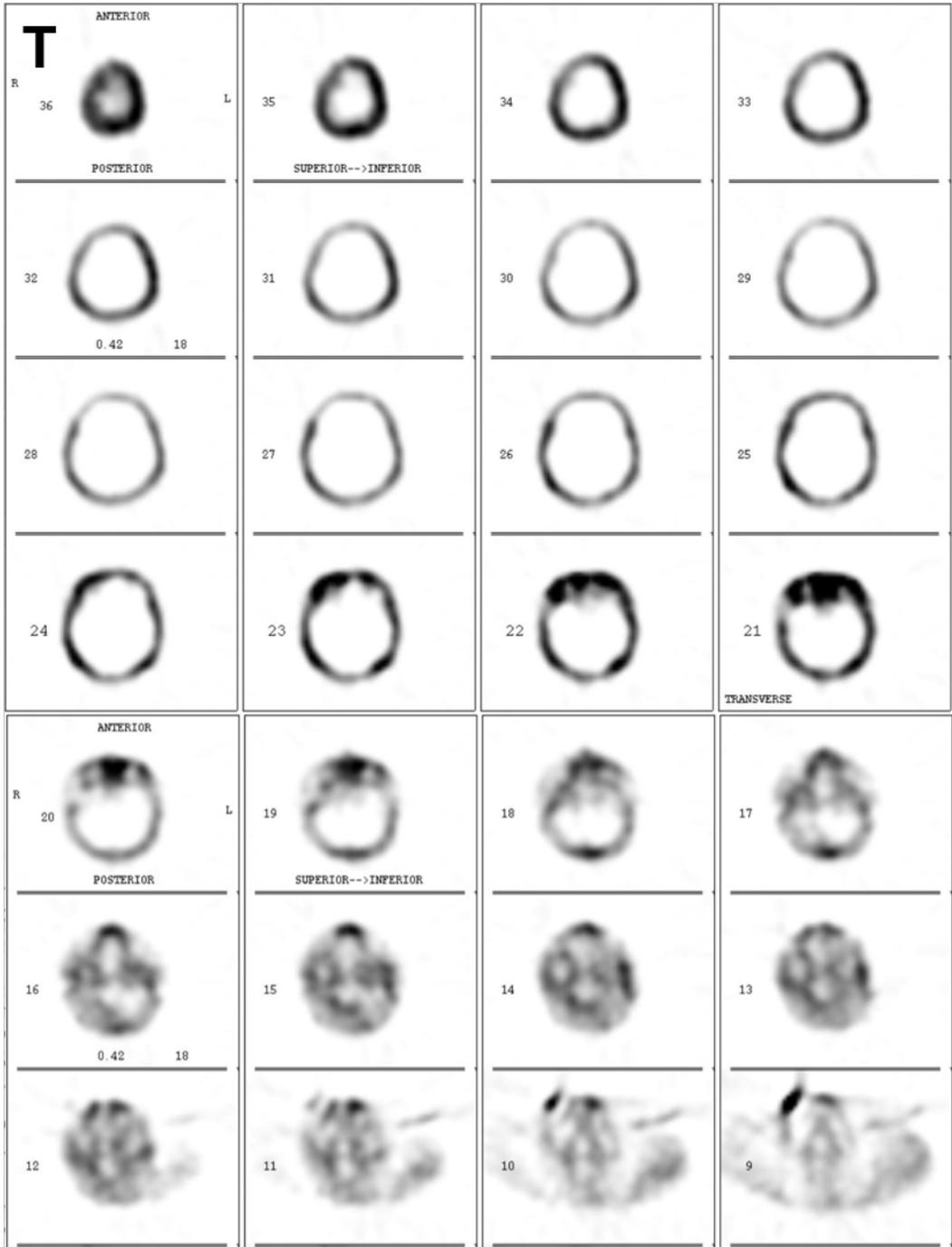
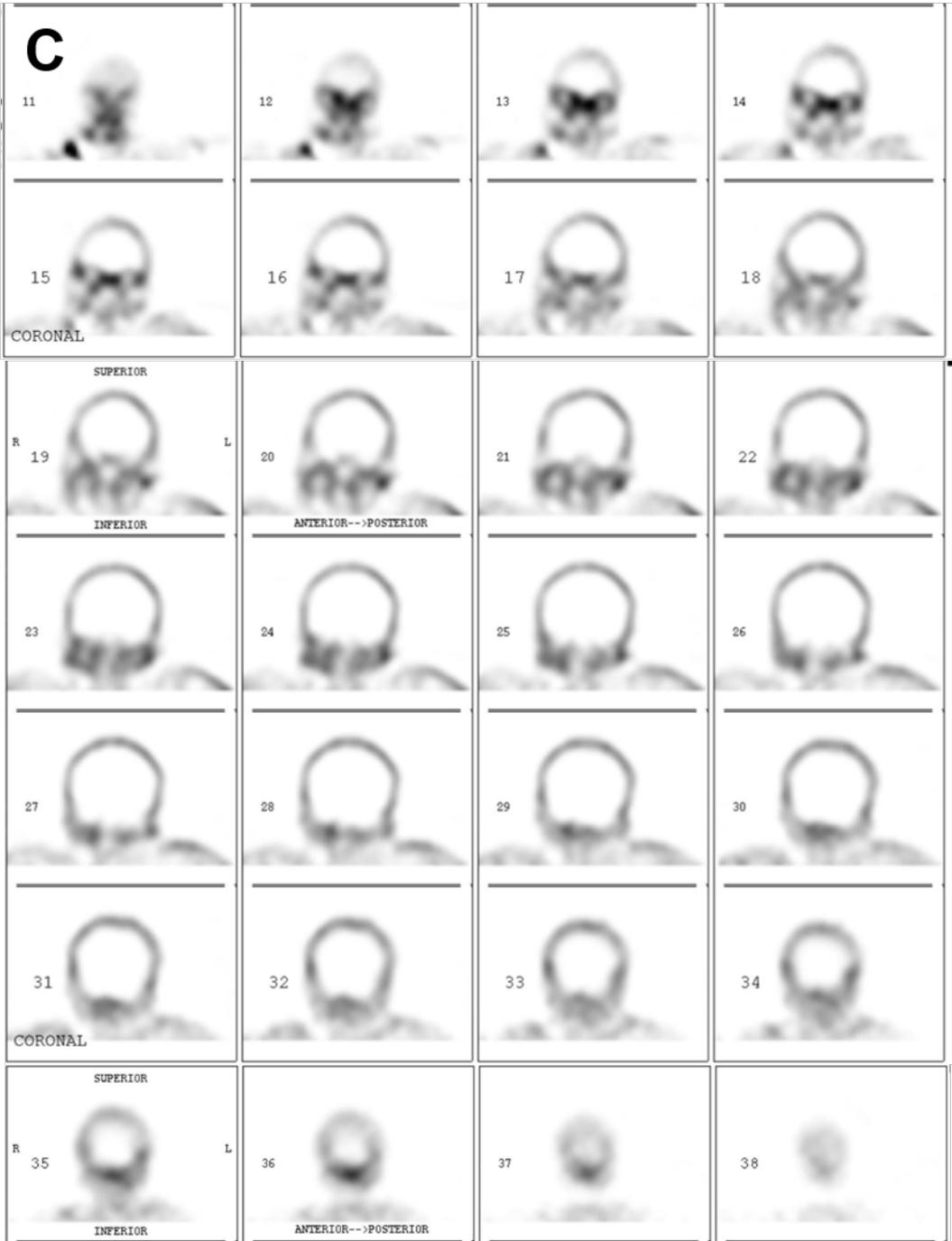
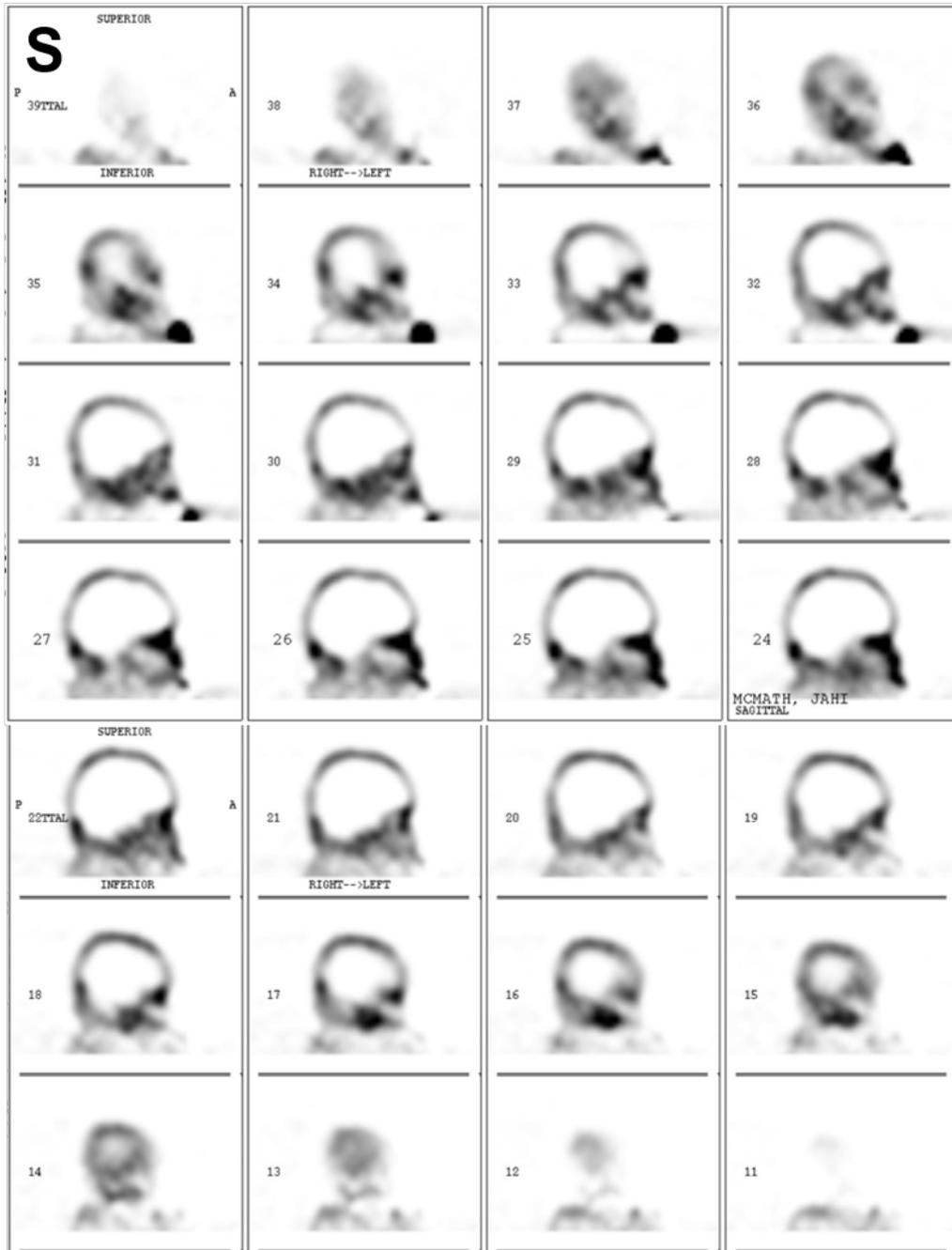


Figure 1. Complete set of anterior 1- or 2- second flow images are presented (time base not stipulated) following injection of 1.0 GBq of ^{99m}Tc -bicisate via femoral central line with scalp tourniquet in place. Common carotid activity is noted however no flow in the cerebral arteries is identified.







Figures 2-4. Transaxial, coronal and sagittal SPECT images are presented as secondary capture images.

No intracranial parenchymal uptake is noted.

Table 1. Chronology

Date	Event	Day #	Comment/details
12.09.2013	Surgery and hemorrhage	0	
12.10.2013	Cardiorespiratory arrest and resuscitation	1	Occurred 12:30 am
12.11.2013	CT evidence of diffuse edema and mass effect; isoelectric EEG; positive clinical examination for BD; apnea test not technically valid (medications not fully cleared)	2	
12.12.2013	Isoelectric EEG; second clinical examination and apnea test satisfy guidelines for determination of BD	3	Death declared 3:00 pm
12.17.2013	Isoelectric EEG; per family request, EEG, CT and records reviewed by an outside neurologist who confirmed BD	8	
12.23.2013	Isoelectric EEG; ^{99m} Tc-bicisate (Neurolite) radionuclide study without evidence of perfusion	14	
12.23.2013	Court appointed neurologist confirms BD with repeated clinical exam and apnea test	14	
01.05.2014	Hospital released Jahi to her mother after authorization from coroner	27	7:00 pm
01.06.2014	Patient admitted to hospital in New Jersey	28	
01.08.2014	Tracheostomy and gastric-tube placement	30	1.0 month
08.25.2014	Discharged to mother's apartment in New Jersey	259	8.5 months
09.01.2014	Portable EEG at apartment reported to demonstrate electrical activity	266	8.7 months
09.26.2014	MRI demonstrated gross preservation of gray matter; MRA and MRV did not show blood flow. EEG at hospital demonstrated no electrical activity apart from "infrequent isolated frontal slowing".	291	9.6 months
04.23.2016	Portable EEG at apartment reported to demonstrate electrical activity	866	28.5 months
05.14.2016	Portable EEG at apartment reported to demonstrate electrical activity	887	29.1 months
10.01.2016	Initial case review in Journal of Nuclear Medicine	1027	2.8 year
06.22.2018	Jahi suffered death by cardiopulmonary criteria	1656	4.5 year

Legend: BD, brain death; CT, computerized tomography; EEG, electroencephalogram; MRA, magnetic resonance angiography; MRI, Magnetic resonance imaging; MRV, magnetic resonance venography.