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^{99m}Tc HM-PAO brain perfusion SPECT in brain death

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Abstract Diagnosis of brain death must be certain to allow discontinuation of artificial ventilation and organ transplantation. Brain death is present when all functions of the brain stem have irreversibly ceased. Clinical and electrophysiological criteria may be misinterpreted due to drug intoxication, hypothermia or technical artefacts. Thus, if clinical assessment is suboptimal, reliable early confirmatory tests may be required for demonstrating absence of intracranial blood flow. We have easily carried out and interpreted ^{99m}Tc HM-PAO SPECT in a consecutive series of 40 comatose patients with brain damage, without discontinuing therapy. Brain death was diagnosed in 7 patients, by recognising absence of brain perfusion, as shown by no intracranial radionuclide uptake. In patients in whom perfusion was seen on brain scans, HM-PAO SPECT improved assessment of the extent of injury, which in general was larger than suggested by CT.

Key words Brain death · Cerebral blood flow · HM-PAO SPECT

Introduction

Early diagnosis of brain death has challenged intensive care specialists, neurologists, neurosurgeons, neuroradiologists and jurisprudential medicine. With the advent of increasingly sophisticated life-support systems and the diffusion of organ donation, needing optimal management of transplantable organs and intensive care apparatus, the physician faces the problem of rapid and accurate recognition of death before irreversible cessation of circulation and respiration.

The "beating heart" body is brain dead only when brain stem functions have irreversibly ceased [1]. The main pathogenetic factor is intense brain oedema with vessel compression, leading to progressive slowing of intracranial blood flow until it ceases.

Clinical and electrophysiological criteria for brain death vary from country to country, but may include: unconsciousness, unreceptivity, unresponsivity, no spontaneous movements, no respiratory effort in response to hypercapnia, no brain stem reflexes (pupillary, corneal, oculocephalic, oculovestibular, oropharyngeal, tracheal); a few legislations insist on a flat electroencephalogram (EEG) and/or no brain stem auditory evoked potentials (BAEPs) [1].

In Italy, criteria for the confirmation of death are based on Law 644, of 2 December 1975, a Decree by the President of the Italian Republic with the force of Law, number 409, of 16 June 1977, partly modified and completed by Law 578 of 29 December 1993. The first article of the last-mentioned states that "Death is identified with irreversible cessation of all brain function", in line with the criteria for the Uniform Determination of Death issued in the United States by the President's Commission for the Study of Ethical Problems in Medicine [2]. There are, however, differences in the criteria for the legal confirmation of death. In cases of circulatory arrest ("cardiac death"),

a period of 24 h is required before the individual can be considered a cadaver. This period can be reduced in cases of beheading, destruction of the body or when a flat electrocardiogram (ECG) is recorded continuously for a least 20 min under the control of an expert physician.

In the ICU, when patients with brain lesions are potential organ donors, the law requires that brain death criteria be used. A committee of appropriate experts (a legal doctor, an intensive care specialist and a neurologist or neurosurgeon expert in electroencephalography) meets and judges whether the patient meets the clinical and electroencephalographic criteria: no spontaneous breathing, no brain stem or spinal reflexes, and a flat EEG. In such cases an observation period of 6 h, during which these clinical and neurophysiological observations are unchanged, is required before death can be declared and life-support systems disconnected. If the patient is not a potential organ donor, the usual practice is to continue ventilation until circulatory arrest occurs, as evidenced by a flat ECG for 20 min. Brain death may be mimicked by intoxication with drugs such as barbiturates and hypothermia or hidden, if reliance were to be placed on the EEG, by electrical artefacts, which are quite common in intensive care units (ICUs) [1]. To overcome limitations in clinical identification of brain death, the use of various imaging studies has been proposed, but conventional techniques, such as contrast or radionuclide angiography and 133-Xenon studies, have limitations of availability, execution, toxicity and interpretation [3–6].

Should interpretation of clinical and electrophysiological criteria be doubtful, the ^{99m}Tc hexamethyl-propyleneamine-oxime (HM-PAO) brain perfusion single photon emission computed tomography (SPECT) may be used [7]. We report a study of patients with serious brain damage examined with this technique, using a commercially available ^{99m}Tc HM-PAO solution [8].

Materials and methods

Forty consecutive comatose patients (25 males, 15 females) underwent a brain perfusion SPECT study, without discontinuation of life-support therapy. The Glasgow Coma Score (GCS) [9] on admission to the ICU was between 5 and 9, the ages between 8 and 82 years.

A dedicated single-detector rotating gamma camera was used, a few minutes after i.v. injection of 950 MBq of freshly prepared ^{99m}Tc HM-PAO, using the following acquisition parameters: parallel hole "general purpose" collimator, 64 step and shoot clockwise planar image acquisition protocol, 15 cm (on average) rotating radius, 20% symmetrical window (centred on ^{99m}Tc 140 keV photopeak), 1.6 × zoom, 64 × 64 matrix, 30–40 min overall acquisiton time. The presence of free ^{99m}Tc was excluded by thyroid region planar nuclear imaging.

During scanning, ventilation was assisted by a portable automatic ventilator and arterial pressure, electrocardiogram and arterial haemoglobin O_2 saturation were monitored by a finger detector.

All patients underwent clinical and electrophysiological examination and at least nonenhanced CT before brain SPECT. One was subjected to MRI after SPECT for comparison purposes.

Table 1 Brain-dead patients in a series of 40 consecutive comatose patients with brain damage (*GCS* Glasgow coma scale, *SAPS* Simplified acute physiology score [11] on admission to ICU)

Patient	Age (years)	GCS	SAPS	Clinical + nonenhanced CT
1	45	5	15	Deep parenchymal haemorrhage
2	34	3	10	Capsular haemorrhage
3	74	6	18	Massive parenchymal haemorrhage
4	72	5	13	Cardiopulmonary arrest
5	43	4	11	Aneurysm rupture with massive parenchymal haemorrhage
6	37	6	9	Postpartum parenchymal haemorrhage
7	13	7	19	Head trauma

Results

In 7 of the 40 patients (Table 1) an early diagnosis of brain death was obtained by a SPECT study showing absence of perfusion of the brain (Figs. 1–5). None of these was a potential organ donor, and ventilation was therefore maintained until circulatory arrest, as described, which occurred between 12 h and 7 days of the SPECT study. Of the 33 patients in whom SPECT did

Fig. 1 Typical brain death on HM-PAO SPECT. Sagittal, coronal and axial images show no intracranial perfusion supra- or infratentorially ▶

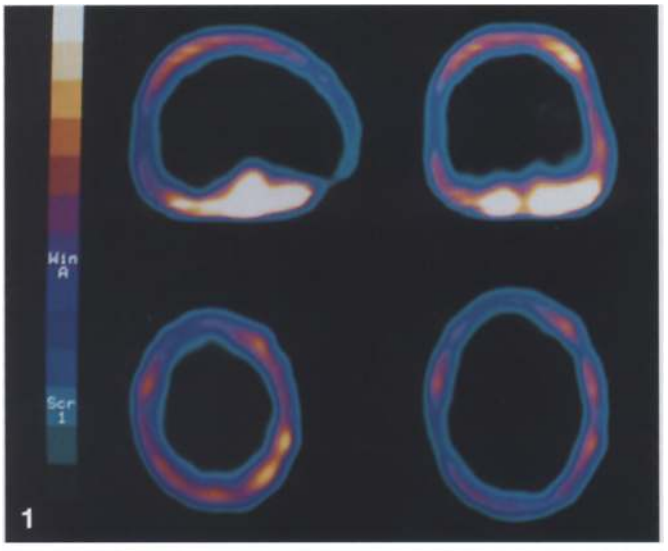
Fig. 2 CT of the patient in Fig. 1, showing a deep intraparenchymal haematoma

Fig. 3 Normal ^{99m}Tc HM-PAO perfusion SPECT study: *upper left* midsagittal, *upper right* midcoronal, *below* axial. Radionuclide uptake is a function of blood flow: higher in grey matter, lower in white matter, absent in cerebral ventricles

Fig. 4a,b Brain death: no intracranial radionuclide uptake. **a** Planar anterior ^{99m}Tc HM-PAO scan. **b** corresponding axial SPECT image

Fig. 6 ^{99m}Tc HM-PAO brain SPECT in suspected thromboembolic stroke. No supratentorial radionuclide uptake; the cerebellum and brain stem are still perfused. The patient was mantained on life-support therapy, but cardiac arrest occurred 24 h later

Fig. 7 ^{99m}Tc HM-PAO brain SPECT in a patient in coma following anoxia. Clinical and EEG data were highly suggestive of impending brain death, but the radionuclide study led us to reject this hypothesis. Ten days later the patient left hospital on foot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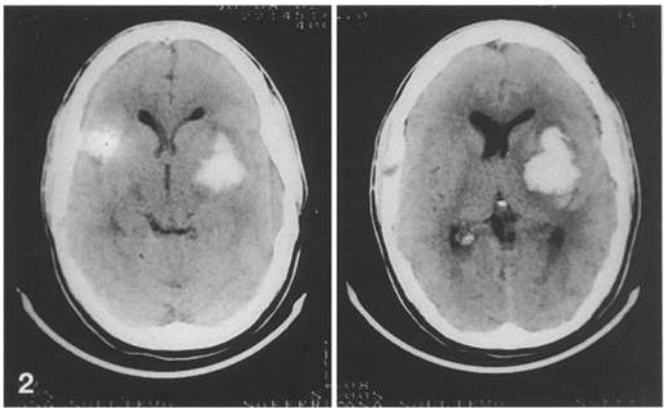
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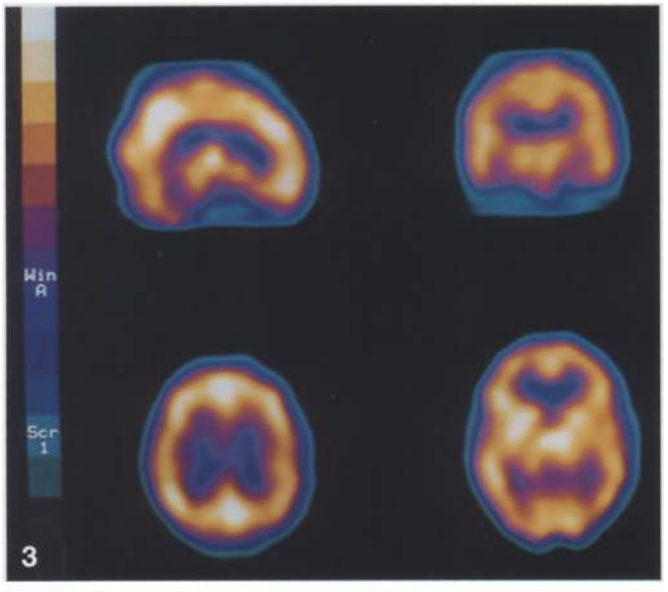
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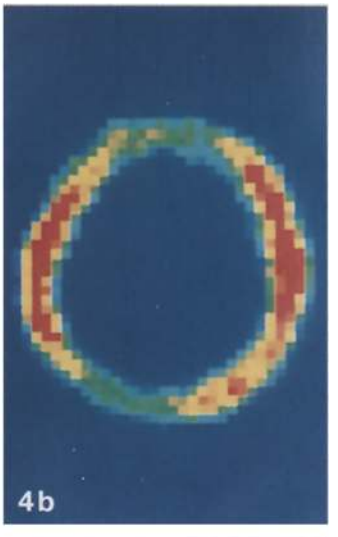
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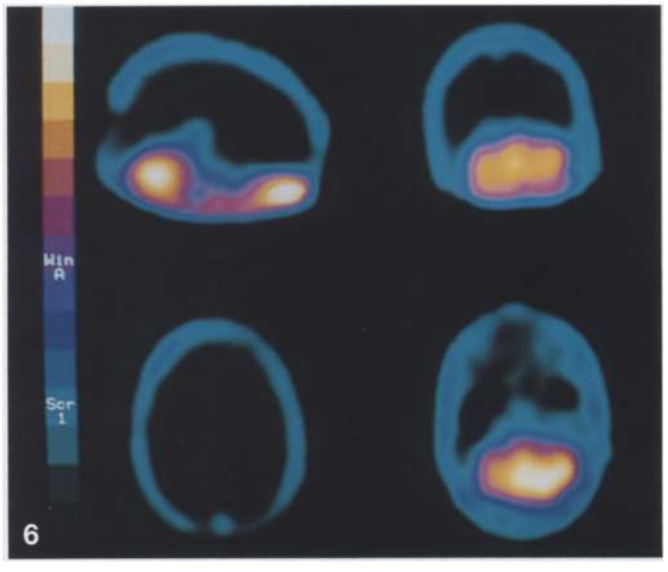
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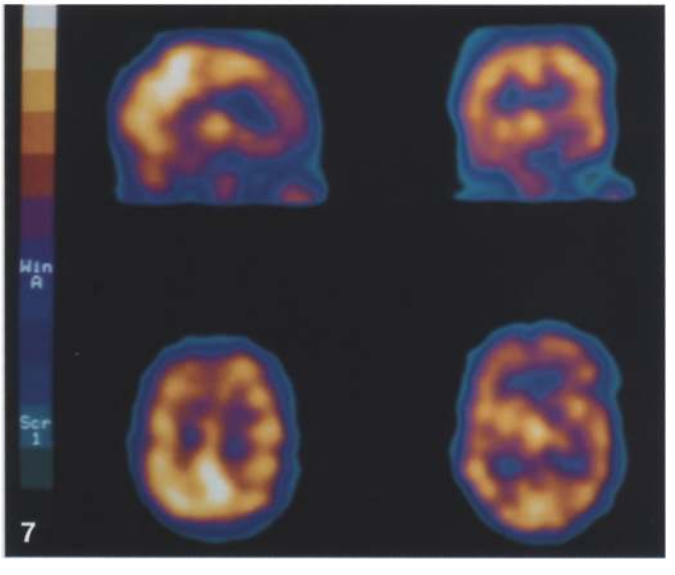
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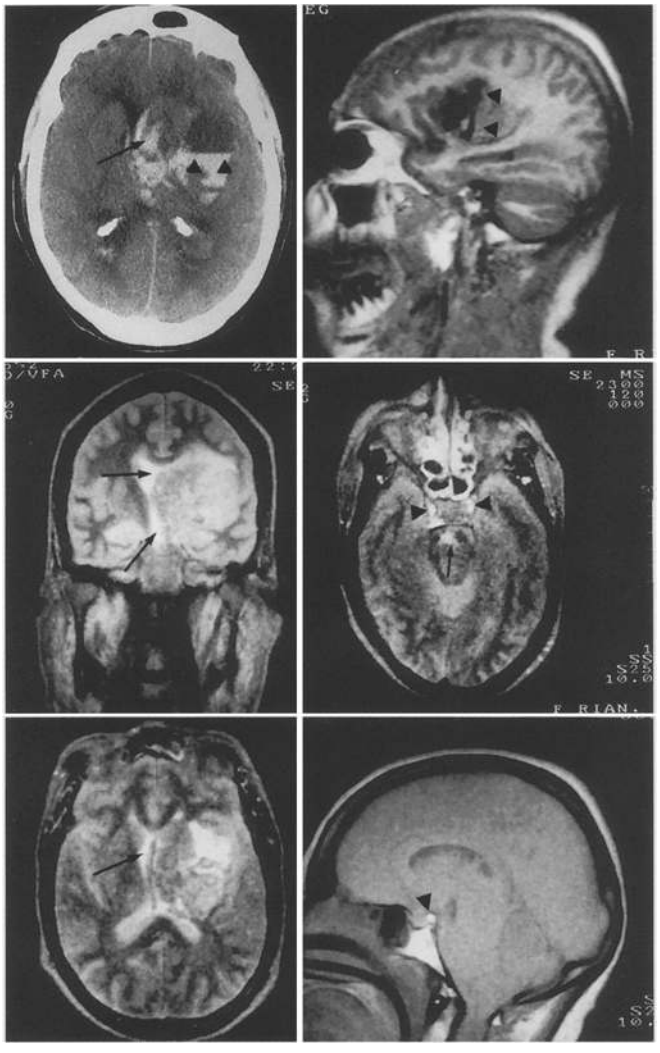

Fig. 5 CT and MRI of patient in Fig. 4. There is a haematoma with a fluid level *(large arrow-heads)* and mass effect and intraventricular haemorrhage *(large arrows)*. Further abnormalities (not visible on CT) are evident on MRI: mesencephalic haemorrhage *(small arrow)*, brain swelling (due to oedema) with loss of the subarachnoid space, and high signal from the major basal intracranial vessels *(small arrowheads)*, suggesting cessation of blood flow

not show total absence of intracranial perfusion, 27 recovered and 6 remained in a persistent vegetative state.

To illustrate the use of brain SPECT, two case histories are presented. A 38-year-old woman with mitral stenosis was admitted for suspected thromboembolic stroke. On admission the GCS was 6 and a CT showed only diffuse cerebral oedema. The patient was put on controlled ventilation and life-support therapy, but her neurological condition did not improve and 24 h later the GCS was 3. Spontaneous breathing and brain stem reflexes were still present. The EEG was not diagnostic due to electrical interference and artefact. Latency lenghtening and lack of IV and V waves were present bilaterally in the BAEPs. A SPECT study (Fig. 6) showed total absence of blood flow supratentorially, while the cerebellum and brain stem were still perfused. Two hours later the patient lost her remaining brain stem reflexes and spontaneous breathing. Cardiac arrest occurred 24 h later.

A 19-year-old woman on dialysis for systemic lupus erythematosis had a sudden cardiopulmonary arrest in the radiology department. In spite of prompt resuscitation, she suffered cerebral hypoxia and was admitted to the ICU with a GCS of 5. In the following days GCS ranged between 4 and 5. The EEG showed low amplitude waves (1–2/s) with periodic burst suppression in the anterior regions and an almost flat trace posteriorly (recording parameters: sensitivity 2.5–3.5 μV, time constant 0.3 s). Brain death was expected in a short time and a SPECT study was performed. Despite the clinically apparent findings the cerebral cortex was well perfused, with only minor diffuse inhomogeneity and relatively low perfusion of the main central nuclei on the left (Fig. 7). The patient recovered completely over the following 10 days.

Discussion

The concept of death has been modified during human history, in line with scientific, cultural and social changes. Until the 1950s cessation of the heart beat and breathing had been identified with death. With the advent and diffusion of cardiocirculatory and respiratory function replacement systems, it is no longer possible to identify death with cardiopulmonary arrest. Intensive care techniques allow a patient who is not breathing autonomously to be kept alive. They also allow a patient to be well oxygenated, with haemodynamic stability for at least a limited amount of time, even if brain functions have completely ceased.

In the last three decades "brain death" has been progressively accepted as complete, definitive cessation of brain function, i.e. the death of the person rather than of the body [9, 10]. This can be recognised clinically by the demonstration of loss of brain stem function.

From a pathophysiological point of view, intense brain oedema leads to an increase in intracranial pressure sufficient to compress intracranial vessels. This explains the arrest of supra- and infratentorial blood flow which is the basis of the scintitomographic picture of brain perfusion (Figs. 1, 4). This picture allows recognition of brain death.

Conventional diagnostic imaging techniques, sometimes used to supplement clinical identification of brain death [3–6], have limitations. Carotid and vertebral arteriography is invasive, not universally available and exposes potentially transplantable organs to contrast

medium toxicity [3, 4]. 133-Xenon brain perfusion studies are even less widely available, do not show the deep structures of the brain and are affected by artefacts from increased extracranial flow [5]. Radionuclide cerebral angiography can be difficult to interpret and is not suitable for the infratentorial structures when performed in the standard anterior view [5, 6].

Although planar ^{99m}Tc HM-PAO scans can show lack of cerebellar perfusion [6], only scintitomographic imaging is adequate to assess brain stem perfusion and should therefore be the radionuclide study of choice if imaging is required for diagnosis of brain death. It cannot be stressed enough that radiolabelling quality control is critical and that a poor radiopharmaceutical preparation can give a false positive diagnosis. Chromatographic checking of the labelling or at least in vivo confirmation of free ^{99m}Tc target organ uptake is needed.

Brain HM-PAO SPECT is easily performed and interpreted [7] and, without discontinuation of therapy, allowed the early diagnosis of brain death in our series. When intracranial perfusion was present, the SPECT study gave a more correct impression of the extent of brain damage, often larger than that suggested by CT.

The case reported in Fig. 6 shows a lack of supratentorial perfusion in the presence of surviving cerebellum and brain stem. This is a recognised situation [5, 6] which probably reflects a step in brain death due to supratentorial lesions. Patients without supratentorial perfusion but intact infratentorial blood flow are not yet brain dead by the accepted criteria, although their prognosis is poor and death may be expected to occur shortly. In this case the SPECT study explained the clinical and electrophysiological findings and confirmed the clinical impression of impending brain death.

The case shown in Fig. 7 stresses the usefulness of SPECT in an opposite situation: a clinical and electrophysiological feeling of impending brain death was contradicted by the nuclear study.

MRI diagnosis of brain death has recently been proposed [10]. We do not consider this the first-choice technique, but rather a valuable approach to the study of the comatose patient with brain damage, in which signs of unsuspected brain death may be present.

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