U. Keske

Strahlenklinik und Poliklinik, Humboldt-Universität Berlin, Augustenburger Platz 1, D-13353 Berlin, Germany

The diagnosis of brain death is one of the most difficult tasks in clinical medicine [1, 2]. Diagnostic criteria and definitions are discussed controversially, not only in the scientific community, but also among the public [3]. The criteria differ from country to country. Some rely on the death of the brain stem only [4], others feel that death of the whole brain including the brain stem is mandatory [5-7].

The diagnosis is largely made clinically [1]. Numerous guidelines exist. The essential parts are tests for volitional activity and checking the patient’s reaction to different stimuli, brain stem reflexes and the apnea test [1]. The most commonly used additive test is electroencephalography (EEG), even though this method is complicated by technical problems and observer errors [2]. Other additional technical investigations may be helpful to make the definite diagnosis, to determine irreversibility and to shorten the time towards a definite diagnosis [2]. Traditional neuro-imaging methods such as computerized tomography (CT) and magnetic resonance imaging (MRI) are not beneficial. Transcranial Doppler sonography is a helpful method for the estimation of blood flow in the base cranial arteries [8, 9]. It is non-invasive and may easily be performed on the intensive care unit. Some authors suggest the use of this test to determine the right time for a confirmatory test such as angiography [2, 10]. Digital subtraction angiography is considered by some to be the most valid sign of brain death [2, 10]. However, it has been postulated that this invasive investigation may be harmful [2]. There have been reports of clinically brain-dead patients with preserved regional cerebral circulation [2].

Scintigraphy methods have played a role in diagnosing brain death for a long time. Dynamic radionuclide angiography has been used since the late 1960s [11-13]. This examination is based solely on the distribution of the tracer in the blood pool, and various tracers, such as technetium-99m-pertechnetate [14], technetium-99m-glucoheptonate [14, 15] or technetium-99m-diethylenetriaminepentaacetic acid (DTPA) may be used [16]. These tracers do not cross the blood-brain barrier [16]. It is a major drawback of radionuclide angiography that blood flow to the cerebellum, midbrain or medulla cannot be evaluated well enough to satisfy the strict criteria for brain death [16, 17]. An exact investigative technique is mandatory. In particular, administration of the radiopharmaceutical as a proper bolus is required [16, 18-22].

Static images obtained with perfusion markers show absent activity in the sagittal and transverse sinuses [14]. Mild sagittal sinus activity may be caused by drainage of the scalp blood via bridging veins [14, 20, 21]. This finding is also known from angiography [20]. In these cases, the diagnosis of brain death may be difficult or even impossible. False positives have not been reported for this technique. False negatives are extremely rare. One such case is described by Hansen et al. [15]. The authors observed radionuclide uptake in a ventricular drain in a clinically and electrically brain-dead patient. The correct scintigraphic diagnosis could be made after removing the drain. Similar problems may exist in patients with a skull defect and may also be found by Doppler studies and angiography [15].

Transcranial Doppler sonography, digital subtraction angiography and radionuclide angiography are methods that examine blood flow in the cerebral vessels. They do not measure brain perfusion directly. This may be achieved by brain perfusion scintigraphy with technetium-99m-hexamethyl propyleneamine oxime (Tc-99m-HMPAO, Ceretec, Amersham). HMPAO is the most...
popular of a group of perfusion markers, which came on the market in the late 1980s. It is a lipophilic radiopharmaceutical which crosses the intact blood-brain barrier and is trapped in neuronal tissue in proportion to regional perfusion [23]. It is taken up by perfused and viable gray matter cells after the initial flow phase. Thus, this tracer directly measures brain function and not simply blood flow. Perfused brain is visualized directly [23, 24]. The uptake is not affected by metabolic or drug status [16, 25]. There is no significant washout [23]. This tracer allows the acquisition of static images, and thus has not the technical problems of radionuclide angiography [16]. Consequently, radionuclide angiography was dropped in most centers after HMPAO became available. Since then, multiple studies have shown the technical feasibility of Tc-99m-HMPAO brain scanning for the determination of brain death [14, 16, 19, 24, 26–32].

With a mobile gamma camera, HMPAO scintigraphy may even be performed on the intensive care unit [16, 18, 19]. In this way, radionuclide angiography and perfusion scintigraphy with planar images may be performed. However, in many countries, this procedure may be difficult to perform or is time-consuming due to legislative limitations.

Generally, planar images are believed to be diagnostic [19, 31, 33]. Anterior and lateral views have to be performed. Several cases have been published where cerebellar perfusion could only be demonstrated in lateral views [28, 31, 33]. The superiority of HMPAO-single photon emission computed tomography (SPECT) over planar images is a well-known fact [23]. SPECT investigations can be performed in the Nuclear Medicine Department only. Among all the studies published on the role of HMPAO-SPECT for the diagnosis of brain death [17, 26, 31–37], only a few are systematic or based on a large population. SPECT images are believed to be superior in the evaluation of the posterior fossa. If the images show preserved perfusion infra- or supratentorially or in one of the hemispheres, the diagnosis of brain death is excluded [17, 29]. However, the prognosis is poor and death may occur within a short time. A repeat study may be indicated [29].

Knowledge about the factors affecting neuronal uptake of HMPAO is essential, since even a 1% false-positive rate is enough to render a test as invalid and of no use to the clinician [1]. Costa et al. [38] found a reduced uptake of HMPAO in lower temperatures and with some medications. Withdrawal of medical therapy such as muscle relaxants or barbiturates is not required for scintigraphy with HMPAO. Although anesthetics can reduce cerebral perfusion, they do not stop it and thus do not interfere with this test [24, 26, 33, 39, 40].

Quality controls for the radiopharmaceutical are very important [32, 41, 42]. Braundau et al. [41] pointed out the possibility of false-positive results due to a labeling failure. These authors suggest in vitro quality control by chromatography and in vivo control by scanning the thyroid gland, lung, and liver of the patient. Grünwald et al. [42] suggest in vivo controls by preparation of a larger amount of tracer and injection of one-half of the vial into a patient who requires brain scanning for clinical purposes. According to recommendations of the German Bundesärztekammer [7], chromatography is required, and additional scans of the chest and abdomen are facultative.

Side effects of HMPAO-SPECT are negligible. However, if organ transplantation is performed after scintigraphy for the diagnosis of brain death, technetium may be carried over to the recipient of the organs and may even be visualized on scintigraphic studies performed shortly after transplantation, e.g., Tc-99m-MAG₃-scintigraphy for the evaluation of transplant renal function [43].

The ideal confirmatory study for brain death should be safe, extremely accurate and reliable, available, quick and inexpensive [14, 19]. HMPAO-SPECT fulfills several of these criteria. A well-written set of guidelines for this test is a very good safeguard against mistaken suspicion [3, 44]. Studies that help to establish these criteria, such as the study of Facco and co-workers in this issue, are extremely helpful in establishing the difficult diagnosis of brain death.

References