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NEUROIMAGING: A WINDOW INTO TOTAL BRAIN DESTRUCTION AND THE UNRESPONSIVE STATES*

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Neuroimaging is the study of the structure and function of the nervous system with techniques that provide anatomical renditions, both static and dynamic, of the nervous system and related structures, information on the physiology of the cerebral circulation, or information on the anatomic distribution over time of biological compounds in the nervous system and related structures. Neuroimaging techniques currently include mainly x-ray angiography, computed tomography (CT), nuclear magnetic resonance – the modality used for magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), magnetic resonance spectroscopy (MRS), diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI) or tractography, functional MRI (fMRI), and perfusion MRI (PWI) – neurosonography, positron emission tomography (PET), single photon emission computed tomography (SPECT) and near infra-red spectroscopy. For the correct interpretation of neuroimaging studies, it is important the correlation of the clinical data with information derived from the various methods used to image the nervous system and related structures.

Neuroimaging in the Neurological Diagnosis of Death

Neuroimaging is not needed for the determination of death by neurological criteria. I prefer not to speak about 'brain death' because the issue is not whether the brain is dead, but whether a human being has died. Additionally, speaking about 'brain death' often confuses the families of the so-called 'brain dead' individual, who end up by asking their physicians whether their loved one – forget about his or her brain – is dead or not [1]. And, to conclude a few considerations on terminology, the terms 'persistent vegetative state' and 'minimally conscious' state are not felicitous. Bernat

* The views expressed with absolute freedom in this paper should be understood as representing the views of the author and not necessarily those of the Pontifical Academy of Sciences. The views expressed in the discussion are those of the participants and not necessarily those of the Academy.

has pointed out how it would be more appropriate to speak simply about a vegetative state, as a neurological diagnosis, and to enter into the prognostic considerations as a separate step [2]. Furthermore, the diagnosis of a vegetative state is not easy to make. Unresponsive patients may have a degree of cognitive activity unsuspected from their motor manifestations. This has been know to be the case in patients with the 'locked-in-syndrome' (a helpful term), but the tools of neuroimaging are now showing that occasional patients fulfilling criteria for the diagnosis of a vegetative state may not be as vegetative after all [3, 4]. Both the terms vegetative and minimally conscious assume that the examiner knows what is going on inside the patient's brain. It would be much better to use terms that denote both the observed phenomenon and its medical cause. For instance, instead of 'minimally conscious', Bernat has proposed the much more sensible term 'minimally responsive'. After all, what we observe is the patient's response. Leaving aside the issue of whether someone can be minimally conscious from a neurobiological viewpoint, the term minimally responsive has the advantage of assuming less about something difficult to measure [5]. The term 'vegetative state' has been consecrated by use, but an alternative, such as 'chronic neurological unresponsiveness' is much more phenomenological and conveys fewer assumptions. It is also more respectful with the patient in this situation.

Although neuroimaging is not usually needed for the determination of death [6], instances where neuroimaging is helpful include:

- When the clinical diagnosis is uncertain
- In cases with important metabolic derangements that cannot be corrected
- When the brainstem is selectively damaged
- When the brainstem function cannot be adequately assessed clinically, such as in cases with massive facial trauma that render it impossible to evaluate adequately the function of the oculomotor and facial muscles
- In very young children
- Some cultures or countries require the use of ancillary tests as a matter of principle and it is legislated that they be used

The ideal confirmatory test of death by neurological criteria should have no false positives, that is, when positive should be incompatible with the recovery of brain function, should not be influenced by drugs or metabolic disturbances (both of which affect the electroencephalogram) and should be easy to apply. Some neuroimaging tests fulfill these criteria, as indicated in a thorough review of the literature from 1966-2005 [7]. Current Canadian standards for the diagnosis of death accept cerebral angiography and

nuclear medicine perfusion studies for this purpose [7]. Perfusion studies with computed tomography or magnetic resonance could also prove to be suitable, but at present they are more cumbersome to perform than nuclear medicine perfusion studies [7].

An important consideration regarding the use of neuroimaging as an ancillary means for the diagnosis of death is how realistically applicable are each of the neuroimaging techniques in the complex intensive care situation surrounding the diagnosis of death by neurological criteria. For instance, the required respiratory and cardiovascular support may not be available at the radiology department where some of these procedures are usually performed. In a study of patients with a recent cardiac arrest and anoxic brain damage, 17 of 27 (63%) patients could not be safely transported to the radiology suite to undergo MRI [8]. If accurate, more mobile techniques that can be used in the ICU would be preferable.

Computed Tomography

CT is used mainly to rule out potentially treatable lesions in patients suspected of brain death. For instance, after head trauma a massive subdural hematoma may be a treatable cause of unresponsiveness. When the process has caused irreparable brain damage, the findings on CT are diffuse cerebral edema with loss of gray-white matter differentiation and transtentorial herniation in about 80% of patients [9]. These findings are not specific for the total destruction of the brain and therefore CT alone helps little in the diagnosis of death. Perfusion CT techniques could prove helpful. For instance in a patient with very severe head trauma arriving intubated to a hospital, CT with perfusion could be used to diagnose both the lack of treatable pathology and the irreversible cessation of brain activity by the lack of perfusion in the entire brain [10]. The absence of internal cerebral vein opacification coupled with the lack of bilateral enhancement of cortical MCA branches have been proposed as characteristic findings of brain death on contrast enhanced spiral CT [11]. Perfusion CT will be greatly facilitated by the new 64-slice multidetector-row CT technology. A 64-slice CT scanner provides high-resolution 3D reconstructions and is capable of acquiring images from the aortic arch to the vertex in 11 to16 seconds [12]. Thus, once the patient is positioned in the scanner, with the appropriate respiratory and cardiovascular support, diagnostic images can be obtained in minutes. There is yet little experience with this technique.

Magnetic Resonance Imaging

As CT, MRI can be used to diagnose treatable pathology in patients with severe brain damage. Even when there is no treatable pathology, MRI renders a clear picture of the status of the brain. For instance, in a man with no brain stem responses after a road traffic accident, on MRI there was diffuse swelling of the cerebral gyri and cerebellar cortex, which showed prolongation of both the T1 and T2 signal with a decrease in apparent diffusion coefficient indicating hypoxic ischemic brain injury, Duret hemorrhages in the midbrain, and downward displacement of the diencephalon and the brain stem, indicating both central and tonsillar herniation [13]. As ominous as these findings are, their specificity is not high enough to define irreversible brain damage. In small series, lack of filling of the major intracranial arteries has been seen on MR angiography [13, 14]. Perfusion MR still lacks specificity defining irreversible tissue damage [15, 16].

Conventional Angiography

An effect of many of the causes of irreversible brain damage, such as trauma or ischemia, is massive brain edema [17]. The molecular mechanisms are still poorly understood, but they involve all cellular components of the brain, including neurons and astrocytes [18]. Neuronal death is accompanied by a cessation of the membrane function consisting of extruding sodium from the neuron. As a result, sodium pours into the neuron and, following the sodium, water. The dead neuron swells, giving rise to what is known as *cytotoxic edema*. Massive brain edema leads to a greatly increased intracranial pressure [17]. When the intracranial pressure rises above the mean perfusion pressure of the proximal cranial arteries, blood perfusion through the brain ceases (*'brain tamponade'*) and quick ischemic destruction of the entire brain ensues. The lack of arterial perfusion of the brain can be imaged by conventional angiography. This procedure requires the injection of a non-ionic contrast media into the intracranial arteries. Each of the two carotid and vertebral arteries are injected through femoral catheterization. Once the patient is in the radiology suite, angiography takes about 20 minutes to perform [19]. This procedure is still required for the neurological diagnosis of death in some countries (e.g., Greece) and it is generally performed once the clinical diagnosis has been made, including the apnea test. The characteristic finding is absent filling of the intracranial arteries at the entry into the skull, although minimal intracranial arterial opacification is

compatible with the diagnosis of death. There should be absent flow in the parenchymal and venous phases of angiography.

Conventional angiography is not without risks, or ambiguities at the time of interpretation of the findings. The procedure is usually performed in the department of radiology, where critical care support may not be sufficient [8]. There is a concern about possible added vasospasm caused by the contrast medium in the intracranial vessels, thus causing cessation of blood flow in vessels that before the procedure remained patent. If the procedure has to be repeated, a local hematoma at the femoral puncture site may prevent repetition. Although unlikely, the contrast medium may cause damage to transplantable organs, particularly the kidneys, of dead donors. Finally, contrast agents could be artifactually introduced into the intracranial circulation with pressure injection or a dependent head, causing the impression of intracranial circulation where there is none [13].

Neurosonography

Circulation in the proximal intracranial vessels can be assessed by means of transcranial Doppler ultrasonography (TCD) and transcranial color-coded sonography (TCCS). An American Academy of Neurology practice guideline about the use of this technique concludes that TCD and TCCS provide important information and may have value for the detection of cerebral circulatory arrest/brain death (Type A, Class II) [20]. On TCD, the normal pattern observed from the flow in the proximal intracranial vessels is of higher systolic peaks and lower diastolic valleys, each peak following the arterial wave caused by the contraction of the heart. Even the diastolic valleys show flow in the arterial direction, of a smaller velocity than during the systolic phase. By contrast, in someone with arrested intracranial circulation, there are brief systolic peaks or spikes followed by an absent or even inverted diastolic flow. Systolic spikes are sharp unidirectional velocity signals in early systole of less than 200 ms duration, less than 50 cm/s peak systolic velocity, and without a flow signal during the remaining cardiac cycle [21]. Transcranial color-coded sonography (TCCS) may show in a vessel the forward arterial flow during the brief systolic peak, coded in red, and, in the same arterial segment, a diastolic reflow, coded in blue (*oscillating flow*). The pulsating flashing pattern is akin to that of a beacon, the *beacon sign* of intracranial circulatory arrest [19]. The Neurosonology Reseach Group of the World Federation of Neurology has published TCD criteria for the diagnosis of

death [21]. Once the clinical diagnosis of brain death has been established, cerebral circulatory arrest can be confirmed if the following extra- and intracranial Doppler sonographic findings have been recorded and documented both intra- and extracranially and bilaterally on two examinations at an interval of at least 30 min.

Systolic spikes or oscillating flow in any cerebral artery which can be recorded by bilateral transcranial insonation of the internal carotid and middle cerebral arteries, respectively any branch or other artery which can be recorded (anterior and posterior circulation). This pattern has to be recorded in at least two different arteries – the vertebrobasilar system counting as one artery.

No signal in the remaining arteries. Transitory patterns between oscillating flow and systolic spikes may be seen.

The diagnosis established by the intracranial examination must be confirmed by the extracranial bilateral recording of the common carotid artery, internal carotid artery and vertebral artery.

The lack of a signal during transcranial insonation of the basal cerebral arteries is not a reliable finding because this can be due to transmission problems. But the disappearance of previously recorded intracranial flow signals in conjunction with typical extracranial signals can be accepted as proof of circulatory arrest.

Ventricular drains or large openings of the skull like in decompressive craniectomy possibly interfering with the development of the ICP are not present.

These are the strictest criteria. Other diagnostic criteria for cerebral circulatory arrest/brain death by TCD have been published, with sensitivity and specificity of 91 to 100% and 97 to 100%, respectively [20]. In a meta-analysis of 280 cases with angiographic confirmation, there were no false positives following the criteria indicated above [19, 21]. However, in some of these studies, angiography was performed first, such that the neurosonographer was not blinded to the angiographic findings [19].

TCD is especially helpful in patients with suspected brain death who have loss of brainstem function due to isolated brainstem lesions or who received sedative or paralytic agents that render clinical examination or interpretation of EEG difficult. Because in some patients ultrasound does not penetrate well the skull (lack of a *'bone window'*) and other technical factors, TCD cannot be performed in all patients. At an institution with experience in neurosonography, TCD may not technically feasible in approximately 10% of clinically brain-dead patients [19].

Radionuclide Angiography

Radionuclide angiography is performed by injecting a radionuclide that remains in the circulatory system of the patient. A gamma camera is used to record the photons emitted by the radionuclide as it flows through the arteries, capillaries and veins of the brain. This intracranial flow is absent when someone has died because of brain destruction. Neuropathologically, six patients without intracranial flow for 20 hours had diffuse brain necrosis and autolysis, whereas six patients with residual flow at the time of radionuclide study had on autopsy less extensive necrosis and evidence of active tissue response [22, 23]. One problem with this technique is that it does not allow a good visualization of the perfusion of posterior fossa structures. For this reason, its sensitivity and specificity have been reported to be 0,97 and 0,67 respectively [24].

SPECT

Single photon emission computed tomography is performed injecting intravenously an isotope, such as technetium, bound to a substance, as HMPAO or ECD, which is highly lipophilic and therefore crosses the blood-brain barrier and binds preferentially to brain. After an injection of one of these substances (^{99}Tc-HMPAO or ^{99}Tc-ECD), the isotope binds to the brain, but clears from the tissues surrounding the brain in less than 30 minutes. Thus, the activity from those tissues does not obscure true brain activity, as happens with conventional radionuclide angiography. As the half life of ^{99}Tc is 6.01 hours, the patient can be scanned several hours after injection, obtaining a snap shot of brain perfusion as it was a few minutes after injection. The patient can be injected in the ICU and images can later be recorded in the Nuclear Medicine Department. There is no need to do tomography: anterior and lateral planar views are sufficient, requiring only about 10 minutes to perform. With a portable gamma camera, images can be obtained even at the ICU.

SPECT depicts regional cerebral perfusion. As there is no perfusion after '*brain tamponade*', a characteristic pattern appears, called the 'empty skull' pattern [25]. Activity in the skull and tissues at the base of the brain outline a space, normally occupied by the brain, that in this case is empty. The finding is so striking that it has also been called 'functional decapitation'. The study of brain perfusion with SPECT agents is more accurate than with radionuclide angiography, because the posterior fossa can be well visualized. In 10 small series, the largest one comprised of 50 patients, there was

not a single false positive in the 193 patients studied [9, 25-33]. SPECT was independently compared to angiography in only 20 patients. In a study without angiographic control, two patients had a flat EEG, but SPECT showed evidence of brain perfusion, ruling out the diagnosis of death.

PET

The findings with metabolic positron emission tomography (^{18}F-fluorodeoxyglucose [FDG] PET) mirror the findings with SPECT. Metabolic activity in the tissues surrounding the ametabolic brain gives the impression of an empty skull [34]. Also with this technique can be clearly shown the functional decapitation that results from total brain destruction. PET is more cumbersome than SPECT for the diagnosis of brain death and it is not generally used for this purpose.

Neuroimaging in the Unresponsive States

Whereas the diagnosis of death based on neurological criteria can be made with a high degree of certainty, based on clinical criteria and, in some cases, with the use of ancillary means such as neuroimaging, the same cannot be said about the so-called vegetative state, which I prefer to call chronic neurological unresponsiveness (CNU). Unresponsiveness or poor responsiveness, as in the minimally responsive state (also called 'minimally conscious state'), usually results from severe brain damage, but there are instances when a surprising amount of brain activity remains in someone who is unable to let others know about it. Almost by definition, a situation such as this would be referred to in the neurological literature as the 'locked-in state'. However, the differentiation of these states requires determining which anatomical structures have been damaged. This determination is carried out with neuroimaging. Neuroimaging provides also a window into some of the mechanisms underlying brain plasticity and recovery, in patients who evolve from chronic neurological unresponsiveness to a minimally responsive state or even to wakefulness.

Chronic Neurological Unresponsiveness (Vegetative State)

Structural brain imaging, such as CT or MRI, is particularly helpful in the acute stage leading to CNU, in order to rule out treatable lesions, such as a subdural hematoma after head trauma. They also provide an image of brain structures in the chronic evolution after severe brain damage. However, CT

or MRI images do not provide information on the activity of the residual brain structures. Regional metabolic activity can be sampled with FDG-PET, typically greatly reduced in CNU [35]. Responsiveness to external stimuli can be better studied with techniques that show transient increases in regional cerebral blood flow, such as water-PET (^{15}O H_2-PET) or the study of the BOLD signal with functional magnetic resonance imaging. Several authors have made the observation that in CNU only the primary cortices become activated with sensory stimulation, whereas in the minimally responsive state also some areas of the association cortex can become active [34, 36].

Using FDG-PET, Schiff *et al*. were able to show a correspondence between metabolically active areas of the brain and the remaining activity observable in each patient. For instance, a 52-year-old man with postoperative asphyxia after cosmetic surgery had been in a vegetative state for 6-months. During wakefulness, he had spontaneous non-directed choreiform movements of the head, trunk and extremities. The authors described this behavioral pattern as a hyperkinetic vegetative state. Structures known to become activated with motor activity, such as the cerebellar vermis, central tegmental region, medial thalamus and the medial aspect of the frontal lobe, had a relatively spared metabolism in this patient. A 49-year-old woman with hemorrhages from a right hemispheric arteriovenous malformation, who had been unresponsive for 25 years, uttered single words in small clusters. This behavioral fragment corresponded to a less-damaged left perisylvian region. Metabolic studies can also show the critical importance of some brain regions for the organization of cortical activity and, therefore, for normal wakefulness. For instance, a 26-year-old male who had been unresponsive for 6 years after a motor vehicle accident had only targetless roving eye movements and posturing (without baseline spasticity) to exogenous stimuli. However, he had near-normal cortical metabolism but damaged medial thalamus and mesencephalon, illustrating the important contribution of these structures to organized behavior [36].

More striking is the recent finding of a normal brain response, detected by functional neuroimaging, in a young woman with CNU [3]. After a traumatic brain injury from a traffic accident occurred eleven months earlier, she remained unresponsive with preserved sleep-wake cycles, in a situation that met criteria for the vegetative state [37]. In an untrained situation, she was given spoken instructions to perform two mental imagery tasks: (1) to imagine that she was playing tennis, and (2) to imagine visiting all of the rooms of her house, starting from the front door. On fMRI, she generated the same BOLD response patterns as the controls, widely different for either task. (3)

Extensive areas of activation, approaching in some cases normal patterns, have been observed in patients in the minimally responsive ('minimally conscious') state [38, 39].

Brain Mechanisms of Recovery: From Unresponsiveness to Responsiveness

Finally, neuroimaging has also been used to try to understand the neurobiological mechanisms that underlie recovery from states of unresponsiveness. Such knowledge could have important implications for the design of more effective rehabilitation strategies. Looking at the entire brain metabolism of a 40-year-old woman in coma after CO poisoning, Laureys studied which parts of the brain were critical for the coordinated behavior of normal wakefulness [40]. Normalization of activity in the superior parietal lobule, including the precuneus, signaled the change from a cyclical unresponsive awakening by day 14 to regaining consciousness by day 19. FDG-PET studies were performed on days 15 and 37. Global glucose utilization remained the same in both scans and it was diminished by 38% compared to 48 normal controls. Laureys attributed recovery to the normalization of activity in the medial occipito-parietal region (MOP) [40]. This area has shown the most consistent impairment in PET studies of the postanoxic syndrome [41].

A recent study shows a neuroimaging pattern that suggests axonal reorganization during recovery [42]. This 19-year-old man had been involved in a motor vehicle accident with closed head injury. After a period of 2 weeks in coma, he was in a vegetative state for several months and had improved to a minimally responsive state in which he had been for 19 years. He was unable to communicate, either by gestures or by words. He made inconsistent head nodding or grunting. Then, 19 years after the accident, he said his first word: 'Mom'. In a few days he had dysarthric but fluent, logorrheic, speech. He was then studied for the first time. He had impaired phonemic and semantic fluency. On MR tractography (diffusion tensor imaging) there were abnormal fibers in the left medial-parieto-occipital region. These fibers were not present in controls. When studied in a similar manner 18 months later, these fibers had disappeared and there was a reorganization toward normalcy of cerebellar vermis fibers [42]. In this period of time, there had been an improvement in logorrhea and in motor function, including cerebellar function. Anosognosia remained [42]. Although this was a carefully designed and interpreted study, more experience with tractography is needed to determine its usefulness in evaluating brain changes in the recovery from the unresponsive states.

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