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The role of neurophysiological methods in the confirmation of brain death

Uloga neurofizioloških metoda u potvrdi moždane smrti

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Introduction

For several decades the medical science society has been in dilemma and debating about when a person is actually considered dead. That a person is dead when his/her brain dies is the attitude of not only medical science, but culture as a whole [1, 2]. The notion that took years to establish of heart being not only the "*primum movens*" but also the "*ultimum morines*", that is that life begins with a heart beat and ends with its arrest, has been abandoned in the last 30 years. From a biological standpoint dying does not recognize the border between the death of the heart and the death of the brain. At the moment of termination of brain function breathing stops as well, and a few minutes or days after, heart failure occurs.

The concept of brain death as the death of an individual, has brought forward many philosophical, ethical, medical, legal and economic issues, and created a dilemma as to when a person is considered dead, from the first report of Mollaret and Goulon in 1959, as a "coma *depasse*" [1]. Soon after that the Harvard Medical School (Harvard criteria of 1968) [1] was the first one to define brain death as an "irreversible coma" which includes the lack of consciousness, spontaneous movement and all reflexes. Since then, the definition and diagnostic criteria have been subjected to significant changes and most of the problems, dilemmas and debates which had before been caused by the concept of brain death due to terminological confusion and great responsibility to declare someone dead with the preserved cardiac function, have been overcome. However, although brain death is now accepted worldwide, diagnosis and diagnostic criteria are far from perfect, therefore further adjustments are needed.

The diagnosis of brain death

Clinical testing is the golden standard and the first step in the diagnosis of brain death. However, the development of medical technology has enabled a more reliable diagnosis and confirmation of brain death using different diagnostic methods, which complement the clinical criteria. Then, when you need to diagnose and confirm brain death quickly and accurately, especially in adverse conditions, diagnostic methods, especially evoked potentials, are very important even though they are not 100% specific and sensitive [1–5]. In patients who meet clinical criteria for brain death, neurophysiological studies have shown that there are "active cerebral hemispheres over the dead brain stem", and *vice versa*. In this regard, it was shown that a female patient was bleeding profusely after cancer surgery in the cerebellopontine angle which led to brain stem death that was proven by clinical tests. Thanks to medical technology, the patient lived another 14 days having the electroencephalographic (EEG) findings similar to those taken during sleep, and normal visual evoked potentials caused by light flashes, which all point to the preserved function of cerebral hemispheres [1].

However, there are significant differences in the guidelines for using diagnostic tests to confirm clinical symptoms. The differences range from the outright rejection of all tests [6] to the acceptance of different neurophysiologic methods and cerebral flow methods, separately or in combination. In addition, differences arise in interpreting the findings and in the time required from the onset of the first symptoms to the procuring of secure evidence that a person is really dead, and that taking cadaveric organs can promptly be carried out.

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Today, in almost all European countries, the diagnosis of brain death is based on clinical, neurophysiologic and cerebral flow methods, except in Britain where only clinical criteria are used for the diagnosis and confirmation of brain death [1]. Additional diagnostic methods for confirmation of the diagnosis of brain death have been proposed by certain national associations in the cause of shortening the waiting period of several days to 6 to 12 h when the removal of cadaver organs can be performed.

Most European countries published recommendations and national guidelines for diagnosis and confirmation of brain death as a prerequisite for removing cadaveric organs. In addition to clinical criteria, in 52 countries of the world diagnostic tests are optional, and in 28 world countries, one of them being Serbia, they are mandatory [1, 7]. Most of them use EEG as a mandatory test that shows the isoelectric line in brain death. According to the recommendations of the American Academy of Neurology (AAN) (2010) for confirmation of brain death, clinical trials are essential and EEG as one of the methods [8].

However, some studies suggest the advantages of multimodal evoked potentials (MEPs) in the diagnosis of brain death compared to EEG [1–3, 9–16]. It is not an invasive method, less sensitive to the effects of sedatives, barbiturates, anesthetics, metabolic disorders, hypothermia, it evaluates the function of the brain stem that cannot be easily clinically examined and the function of the cerebral cortex and in comatose patients. So, it can provide useful information about clinical findings of the function of the brain stem and cerebral cortex and in adverse conditions without changing its parameters (latency, amplitude and morphology of the wave), which is not the case with the EEG [17, 18]. These tests are safe, accurate and they significantly improve and accelerate the procedure of taking the cadaver [11, 12, 19–23]. The significance of evoked potentials in the diagnosis of brain death is presented in the research done by Facco et al. [24] 2002. On a group of 130 patients diagnosed with brain death, the authors show the absence of auditory evoked potentials (AEPs) and in 92 patients, the presence of only I or I and II AEPs waves in 32 patients. However, in 6 patients III and V waves were still present, which excludes the death of the brainstem. The same authors [24] showed the presence of N9 and N13 waves (responses of the brahialisa plexus and cervical spinal cord segments) in 122 patients and the absence of N20 waves (cortical response). However, in 4 patients P14 or N18 waves were registered, which are generated in the brainstem therefore excluding brain death. Thus, the combined use of AEPs and somatosensory evoked potentials (SEPs) confirmed brain death in 93% of patients and have demonstrated a residual activity of the brain stem in 6 patients of which 3 met all EEG and clinical criteria for the entire brain death. The authors conclude that the combined use of EEG's, AEPs and SEPs significantly improves the diagnosis of brain death.

In 2009, Djuric et al. [14] published similar results in a group of 84 patients with clinical criteria of brain death. In 10 (11.90%) patients EEG showed certain cortical activity in the form of alpha, tetha and delta waves, AEP showed I, II and V waves in 3 (3.57%) patients, and median SEPs in 5 (95%) patients, which all exclude brain death. The authors conclude that EEG as the only method in confirming brain death is not sufficient.

Electroencephalography

The first applied neurophysiological method of brain death confirmation was EEG. It found its place in one of the few, widely-used and cited regulations for confirmation of brain death (Harvard, 1968) as a "mandatory" criterion [5]. At that time, it was the only available diagnostic method which could investigate the function of the brain and confirm brain death. However, ten years later the American Association of Neurology degraded this method from "mandatory criteria" to "useful indicator" for several reasons and this was proven by a number of research [3, 14, 25–27]. Heckmann et al. [26] showed that a 53-year-old patient with ischemic encephalopathy after cardiopulmonary arrest with spontaneous superficial respirations and the preserved cerebral perfusion on his EEG had an isoelectric line. He lived for another 7 weeks.

Regarding the application of EEG methods in confirming brain death, there are arguments "against" and arguments "for" its application.

Arguments against the application of EEG are:

1. EEG records the spontaneous bioelectric activity of the cortex to the depth of about 5 mm, so it is not an informative method for the detection of the brain stem function.

2. EEG does not show the function of neurons of the basal bark, interhemispheric fissures and deep sulci.

3. EEG can be a useful method when we do not accept the concept that the "brain stem death is the death of the individual", because studies have shown that patients with a dead brain stem have some electrical activity in the EEG within 48 hours [4, 28].

4. Technical problems arise in the intensive care units in which most often the brain death is confirmed due to an abundance of artifacts caused by the work of respirators, monitors, and the like, which make it difficult to identify electrocortical activity.

5. EEG can give false positive and false negative findings. Studies have shown that the isoelectric line on EEG heads to the erroneous diagnosis of brain death (with the comatose or vegetative patients after prolonged cardiac arrest, in sedation, hypothermia and metabolic disorders), and conversely, the preserved electrocortical activity in EEG gave false hope that the person is alive, according to clinical criteria of the dead brain stem [10, 13, 14, 29, 30] (Figures 1 and 2 [15]).

For these reasons, further investigations are directed towards the implementation of other more recent neurophysiological methods with different modalities of evoked potentials. Numerous studies proved that the isoelectric line on EEG is not a reliable evidence of brain stem death, because the acoustic evoked potentials in these patients were almost normal [3, 27, 29–32].

Despite these limitations, EEG is recommended in all countries that have adopted the definition of "the entire brain death", even so in the regulations applied in Serbia, as one of the auxiliary methods.

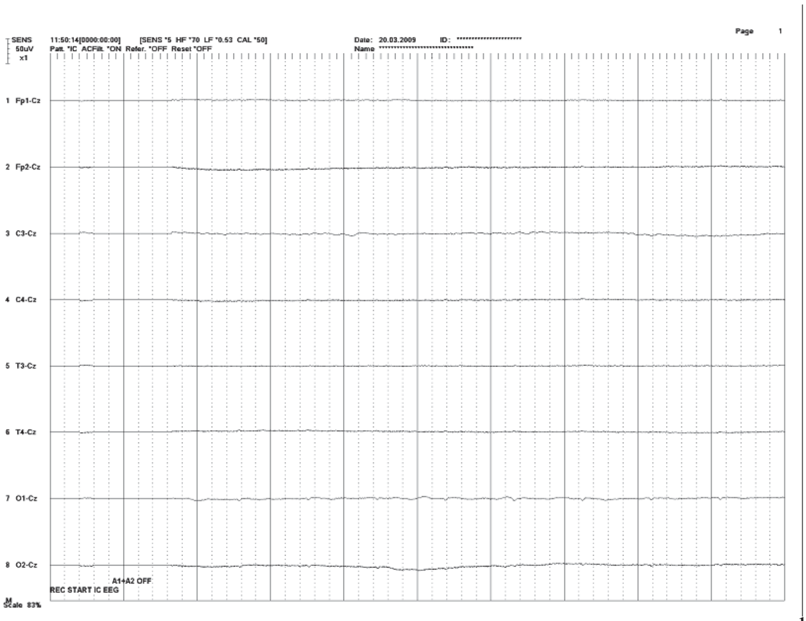

Fig. 1 – Electroencephalography (EEG) shows the isoelectric line in brain death [15]

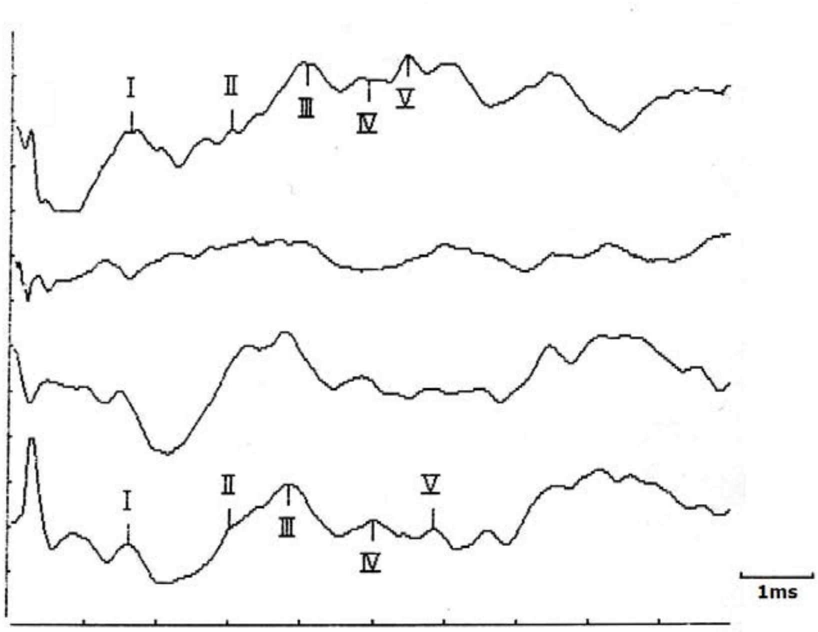

Fig. 2 – Auditory evoked potentials (AEPs) show almost normal findings [15] in the same patient whose EEG is described in Figure 1

When should we be careful in interpreting the EEG findings? The answers are as follows:

1. With medication intoxication in which case the isoelectric line can be maintained up to 50 h after poisoning with complete recovery.
2. After cardiac arrest and global cerebral ischemia, where the isoelectric line on EEG can be maintained for hours.
3. In adverse conditions such as hypothermia, metabolic disorders and apallic syndrome. In these states the electrocortical activity in the cortex is lost much earlier in relation to evoked potentials
4. In vegetative state

Auditory evoked potentials of the brain stem

Clinical application of this test is based on the evaluation possibilities of the acoustic system functions from the inner ear to the midbrain. In recent years, among other indications, these tests have been intensively applied in comatose patients as well, because of the resistance to the effects of barbiturates and anesthetics, and they hold a special place in the protocols for confirmation of brain death [31].

Numerous studies have determined AEPs findings indicating brain death. A typical finding of this test is the bilateral presence of only I and/or I and II waves, or rather, the absence of all waves (Figure 3) [10, 11, 31, 33]. We should bear in

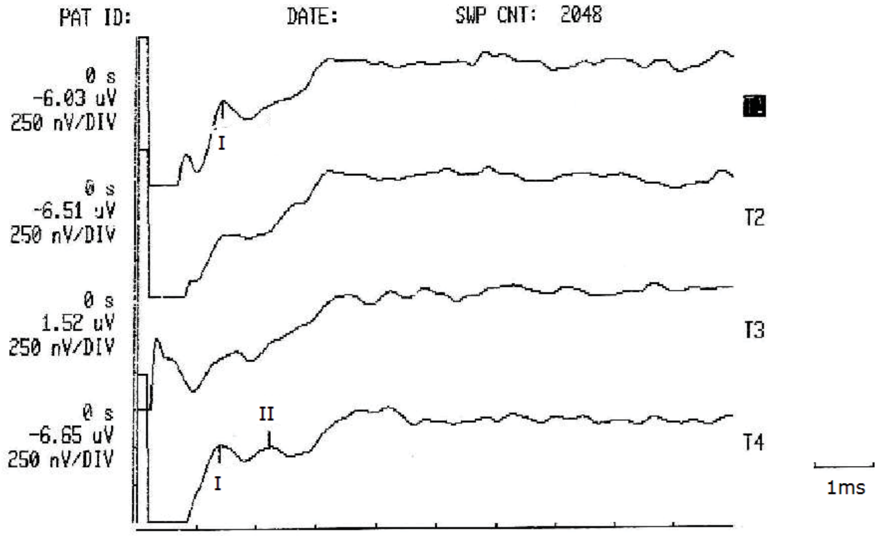

Fig. 3 – Auditory evoked potentials (AEPs) findings indicate brain death in the patient (I and II waves are present) [11]

mind that an I wave can be absent with hemorrhage in the inner ear, temporal bone fractures that can cause damage to the bone labyrinth and deafness which existed prior to the brain death.

Research done by Facco et al. [24] shows that 70% of brain dead patients had a straight line on AEPs as a proof of circulatory disturbance and in the cochlea which occurs after the cerebral flow cessationh. When AEPs findings are sequentially registered during the dying process, disappearance of the waves shows that the final image, i.e. the flat AEPs is the result of patient's death, thus confirming their diagnostic value. In contrast, AEPs play a key role in excluding false positive findings in comatose patients when the brain seems dead. In this regard, the absent brainstem reflexes and a flat EEG with intact AEPs were found in 4.5% of patients even in the absence of sedation or other reversible effects of coma, which confirms their advantage over the EEG and clinical criteria in excluding brain death. By using a combined application of AEPs and SEPs, the authors [24] have confirmed brain death in 93% of patients.

Somatosensory evoked potentials

Microcomputer technology and modern multichannel appliances for evoked potentials, allowed the intensive clinical use of this modality in the last 30 years. As a result, the method has taken its important role, not only in diagnostic process of neurological diseases, but also in protocols for determination of brain death. A typical finding in the brain stem death or brain hemispheres death is a normal potential over the brachial plexus (N9), the normal potential of the 7th vertebra [3] and the lack of response of thalamo-cortical projections and the somatosensory cortex (N20-P25 complex) [15, 22, 23].

Past research, as well as a 15-year experience of the author [25], have shown that this electrophysiological test is very reliable in confirming brain death, because it is the least sensitive to technical problems in the intensive care unit. This test allows the evaluation of the conductivity at the cervico-medullary level. Therefore, an analysis of the waves that are generated in the brainstem is needed. In brain death SEPs should be registered by using the non-cephalic reference electrode in order to register the "far field" potentials (P14 and N18) which are generated in the brainstem at the level of cervico-medullary circuit, medial lemniscus and nucleus cuneatus. The routine use of frontal reference electrode – Fz shuts down all the "far field" waves and allows only the assessment of cerebral cortical function, as is the case with the EEG, so it is there possible to verify the presence or absence of the activity of the somatosensory cortex, which is insufficient for the confirmation of brain death.

Therefore, SEPs with a non-cephalic reference electrode provide important information about the function of the medulla oblongata and the cervical-medullary circuit, which could lead to the improvement of criteria for the diagnosis of brain death. Therefore, a combined use of AEPs and SEPs provides testing of ponto-mesencephalic and bulbar levels until the death of the entire brain stem. With dying patients the disappearance of P14 and N18 waves is closely time-associated with the disappearance of the reflex to bronchial stimulation and the appearance of apnea. In fact, the apnea test would be an unthinkable harmful procedure in comatose patients, because it can lead to a serious increase in intracranial hypertension. For these reasons the apnea test should be the last test in the process of confermation of brain death after the disappearance of the evoked responses generated in the brain stam[14, 24].

Visual evoked potentials

Visual evoked potentials (VEPs) represent the neurophysiological method for examining the function of the visual pathway from the retina to the occipital cortex.

This method is often superior to ophthalmic and neurological examination because it shows not only clinical but also subclinical lesions of the optical path. That is why it has been applied in the last several decades in the diagnostic processes of ocular and neurological diseases. It is also useful for the confirmation of brain death, where a special stimulator with a flashing light in the form of spectacles is used. A response is recorded over the visual cortex and beneath the lower eyelid for recording the responses of the retina. VEPs with the simultaneous registration of electroretinogram may be a sensitive indicator of an early impairment of cerebral function. It shows the function and the subcortical structures which make it more sensitive than EEG.

The test is easily performed and is highly resistant to technical artifacts in the intensive care units. It provides useful information about the function and the integrity of the visual pathways. It is important in the differentiation of cortical and brain stem lesions [32]. With brain death a response of the retina is always present (Figure 4) [10, 15].

Conclusion

Neurophysiological methods are important in confirming brain death. In the recommendations and the national guidelines in most countries of the world, these tests are optional, and a smaller number of countries consider them obligatory, Serbia being one of them. EEG, applied as the first and most commonly used neurophysiological method, is not sufficiently reiable in confirming brain death, because it does not show the function of the deeper structure of brain hemispheres and brainstem, but rather of the cortex only. The application of evoked potentials, however, provides more information about the function of multiple afferent pathways of the brainstem and hemispheres. On the other hand, evoked potential tests are less sensitive to the so-called adverse conditions such as metabolic disorders, intoxication, coma, hypothermia, anesthesia, and similar, compared to EEG. The complemenary application of these methods is more reliable in confirming brain death.

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