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Editorial

Spinal reflexes and brain death

Focardi et al. (2022) describe a patient suspected of meeting diagnostic criteria for brain death, who demonstrated an unusual response of slow bilateral eyelid elevation in response to painful stimulation of both the right and left nipple. It was determined that the observed eyelid elevation was due to preserved function of sympathetic fibers arising from the superior cervical ganglion located in the neck, which innervate the superior tarsus (Mullers) muscle, and not due to preserved function of the oculomotor nucleus in the midbrain and its associated oculomotor nerve, which innervates the levator palpebrae superioris (eyelid elevator) muscle. This was concluded based on (i) repeated clinical assessment showing apparent loss of oculomotor nerve function including unresponsive pupils and absence of oculovestibular reflex, along with brainstem areflexia and apnea more generally, (ii) loss of facial grimace or other pain response, (iii) recognition that the eyelid opening was slow, consistent with smooth (Mullers) and not striated (eyelid elevator) muscle, and (iv) additional findings consistent with brain death from ancillary tests including angiography and electrophysiology. Therefore, the observed eyelid elevation in response to thoracic stimulation was considered an extracerebral reflex involving the spinal cord and sympathetic fibers from the superior cervical ganglion, and not evidence of brainstem function; hence it did not preclude the diagnosis of brain death in this case.

Although eye opening in brain death is quite rare, it is part of a broader class of movements seen in patients diagnosed as brain dead, known as spinal reflexes (Greer et al., 2020) or as brain death-associated reflexes and automatisms (Jain and DeGeorgia, 2005). I will here review movements in brain death and their relation to the spinal cord, as prompted by the case study.

Interestingly, when the Harvard Ad Hoc Committee published its recommendations for determining brain death in 1968, they emphasized that "*we are concerned here only with those comatose individuals who have no discernible central nervous system activity*"; and stated that the patient must have "*No Movements or Breathing*" (Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death, 1968, p. 337). Thus, any movement, any spinal reflex, would preclude the diagnosis according to these criteria.

Today, the diagnosis of brain death is not precluded by spinal activity. In fact, many reflexes, automatisms, and complex movements are considered consistent with the diagnosis of brain death. They are not uncommon, having been reported in 13–75 % of brain death patients (Greer et al., 2020, Supplement 4). Such movements include: finger and toe jerks, undulating toe flexion, triple flexion, increased tendon reflexes, plantar flexion, myoclonus, repetitive leg movements, spontaneous abdominal contractions, head turning, decerebrate-type movements, extensor posturing, eyelid opening, fasciculation, hugging movement, thumbs up sign, respiratory-like movements, pronator-extension, limb elevation, and the "Lazarus sign", or shoulder adduction and bilateral arm flexion raising to the chest with dystonic posturing of fingers, as if arms are crossed over the chest, or as if grabbing the endotracheal tube (Greer et al., 2020, Supplement 4).

In all these cases, the movement has been considered solely of cord origin, with no brainstem involvement. And yet – unlike the case of eye opening described by Focardi and colleagues (Focardi et al., 2022) – the mechanism is often not known, particularly for complex movements. In a review of movements in brain death, Saposnik et al. (2009) wrote "the pathophysiological basis of [many movements in brain death] has remained speculative … We can only propose … possible mechanisms … unfortunately, there are no well-documented human studies demonstrating these phenomena" (Saposnik et al., 2009, p. 158). Jain and DeGeorgia wrote "Although evidence points to a spinal origin for such movements, the pathophysiology in many cases remains speculative" (Jain and DeGeorgia, 2005, p. 122).

The interpretation of these movements as solely of spinal origin has not gone unchallenged. In an in-depth assessment of the World Brain Death Project's report on the determination of death by neurologic criteria (Greer et al., 2020), Joffe, Hansen, and Tibballs (Joffe et al., 2021) evaluate the claim that all these movements are exclusively cord-generated. (Some of them clearly are. The question is whether *all* are properly attributed to the spinal cord without supraspinal contribution.) The complex polysynaptic reflexes mentioned above are often attributed to central pattern generators in the spinal cord that, when tonic supraspinal input is removed, are "released", creating hyperexcitability at the spinal level and allowing the movements observed during brain death (Jain and DeGeorgia, 2005).

Joffe and colleagues offered several reasons to doubt this explanation. Such complex movements have never been described in acute spinal cord injury or transection; in the setting of spinal injury, central pattern generators are not active in the acute phase and take days to weeks to return to functioning, which is beyond

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the window when these movements are seen in brain death; human spinal pattern generators produce rhythmic movements, not the sustained single actions seen in brain death; when spinal mechanisms are responsible for the rhythmic actions seen with pattern generators, muscle movements are very small, unlike many of the brain death associated movements; spinal automatisms, including "walking movements", do not occur in primates with complete cord injury unless some stimulation (electrical or pharmacological) is provided to replace the tonic supraspinal input; finally, the initiation and modulation that brainstem mechanisms provide over central pattern generators are particularly important for flexor muscle activity and bilateral arm movement coupling. "All of this suggests that so-called complex spinal reflexes in [brain death] are most likely due to clinically observable brainstem function" (Joffe et al., 2021, p. 100).

Therefore, no mechanism has been postulated that satisfactorily explains all observed movements in brain death in terms of spinal cord activity without supraspinal input, and existing proposals for such explanations are acknowledged as speculative at best. It is not known that so-called spinal reflexes in brain death are, in fact, of spinal origin; some may reflect residual brainstem function.

In the case of slow eyelid elevation in response to thoracic stimulation, Focardi et al. have suggested that cerebral flow evaluation should be used as a prudential measure, and it should show absence of intracranial blood flow prior to determining brain death (Focardi et al. 2022). This is a reasonable approach, but it should be interpreted with caution, as false negatives can occur with any modality (i.e., the test shows intracranial circulatory arrest – it is negative for blood flow – yet some brain function or blood flow continues). For example, in one case an adult exhibited return of cough reflex, intermittent spontaneous breathing, and extensor posturing after diffusible radionuclide cerebral perfusion SPECT imaging showed no intracranial flow (Latorre et al., 2020); in another a young child demonstrated return of spontaneous breathing after non-diffusible nuclear medicine test showed no intracranial blood flow (Shewmon, 2017). Jahi McMath was an adolescent who received continued treatment for more than 4 years after being declared dead by neurologic criteria (Shewmon, 2018). In her case, diffusible radionuclide imaging showed absence of brain blood flow, yet structural imaging 9.5 months after being declared brain dead demonstrated large areas of structurally intact brain tissue, which is inconsistent with the absence of brain blood flow for that period of time (Shewmon, 2018). Furthermore, half of patients declared to be brain dead have preserved osmoregulation (Nair-Collins and Joffe, 2021a). This demonstrates arterial flow and venous drainage from magnocellular cell bodies in the hypothalamus as well as the posterior pituitary (Nair-Collins and Joffe, 2021b). This has been observed even when imaging shows intracranial circulatory arrest (Nygaard et al., 1990; Varelas et al., 2011; cf. Nair-Collins and Joffe, 2021b for discussion).

Finally, "diagnosis creep," that is, broadening a diagnostic category so that more people will fall under it, is a significant concern in this context. It would mean declaring a patient to be dead, even though they do not meet established criteria for brain death. Fattal and colleagues (Fattal et al., 2020) report a case in which a patient almost met criteria for brain death, except for subtle spontaneous vertical eye movements. While they delayed the diagnosis until cessation of eye movements, they suggested that "such a subtle and limited finding, even though reflects residual brainstem activity, yet in the context of the complete exam, is still compatible with brain death" and that "organ donation should not be delayed for fear of organ deterioration" (Fattal et al. 2020, p. 1). They claimed that findings in this case are compatible with brain death, based on 2010 guidelines from the American Academy of Neurology (Wijdicks et al., 2010). They are not: eye movement is explicitly inconsistent with the diagnosis, for the reason the authors stated, namely, it reflects residual brainstem activity (Lewis and Greer 2020). If residual movements in brain death are attributable to the brainstem, then that movement is inconsistent with the diagnosis and the patient is not dead. Physicians should not seek to broaden the category of brain death "for fear of organ deterioration", but instead should seek to be worthy of public trust in determining death.

To conclude, a variety of movements may be seen in patients suspected of brain death. In the case described by Focardi and colleagues, slow bilateral eyelid elevation in response to thoracic stimulation can be attributed to the spinal cord and sympathetic fibers arising from the superior cervical ganglion. However, the underlying pathophysiology of other movements in brain death is unknown. Some suggest that they may be attributable solely to spinal central pattern generators, while others argue that they likely reflect brainstem involvement. This is an important area of research: if any of the movements seen in suspected brain death reflect brainstem involvement, then the justification for declaring a patient exhibiting those movements to be "dead" is called into question.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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