Clinical Reasoning:

A 76-year-old man remaining comatose after cardiopulmonary resuscitation

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SECTION 1

A 76-year-old man was admitted to the hospital after having a “cardiac arrest” while riding his bicycle and subsequently falling into a canal. Thirty minutes after the accident, he was resuscitated by an ambulance crew. They detected a ventricular tachycardia, which responded to defibrillation. Thereafter, there was a sinus bradycardia, which was treated with atropine and adrenaline. After 30 minutes of resuscitation, there was return of spontaneous circulation (ROSC). At admission to our hospital, the patient was comatose, with a body temperature of 30°C and Glasgow Coma Scale score (GCS) of E₁M₁V₁. According to protocol for presumed acute hypoxic ischemic encephalopathy, therapeutic hypothermia was started. The body temperature

of the patient was kept at 32°C to 34°C for 24 hours. A few hours after starting hypothermia, twitches around the eyes and mouth were noticed and a neurology consultation was requested. Neurologic examination during hypothermia and under sedation showed a deeply comatose patient with intact pupillary reaction to light bilaterally and present oculoccephalic reflex. He had multifocal random twitching movements involving the face, arms, and legs. These shock-like movements were found to increase as a result of external stimuli.

Questions for consideration:

1. What are the possible causes for the twitches?
2. What diagnostic test would you order?

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SECTION 2

The twitches could be myoclonic jerks as a consequence of severe hypoxic brain injury, a myoclonic status epilepticus, or a manifestation of acute provoked epileptic seizures. An EEG, which could help to differentiate among these conditions, showed generalized slowing of cerebral activity. There were also periodic sharp wave discharges at 1 to 2 Hz over the parieto-occipital regions on both sides, without evolution in their amplitude or frequency and with no correlation to the random twitches around the eyes and mouth. This resulted in a diagnosis of severe hypoxic ischemic encephalopathy with nonepileptic myoclonic jerks. In myoclonic status epilepticus, a close correlation is expected between the EEG discharges and the clinical jerks.¹ Burst-suppression pattern and presence of generalized epileptiform discharges on EEG, when present, are also known to predict poor outcomes but with insufficient prognostic accuracy (evidence level C).² The patient received a loading dose of sodium

valproate 20 mg/kg, followed by a maintenance dose of 40 mg/kg/d. However, the myoclonic jerks became more pronounced, which was distressing for the patient's family to watch and also made nursing care difficult. He was then treated with infusions of propofol and midazolam, which resulted in the subsidence of the myoclonic jerks. After 24 hours, hypothermia was stopped according to protocol and the patient was rewarmed over 12 hours to 37°C. On the third day, the jerks disappeared and the sedative medications could be stopped. The patient became normothermic but remained comatose with a GCS of E₃M₁V_{tube} with intact pupillary, corneal, and oculocephalic reflexes. The neurologic examination was done more than 30 minutes after sedatives were stopped.

Question for consideration:

1. What test would you order to help determine the patient's prognosis?

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SECTION 3

According to an evidence-based guideline of the American Academy of Neurology (AAN),² somatosensory evoked potential (SEP) testing could help to determine this patient's prognosis. A SEP study of the median nerves was done on the fourth day of hospitalization. The patient was normothermic and without sedative medications for at least 12 hours at the time of this test. There was no evidence of other confounding factors such as injury to the cervical spinal cord. The SEP results are shown in the figure. The first channel shows the response at Erb point, and the second one is recorded at the level of C7 cervical spinous process. The last 2 channels show responses from cortical electrodes, ipsilateral and contralateral to the stimulus point, respectively. An additional

test that could be done in this context is the determination of serum levels of neuron-specific enolase (NSE). Elevations of NSE are associated with increased severity of postanoxic neuronal injury.³ However, more recent studies suggest that this test has a limited predictive value for outcome.^{4,5} Data from studies on brain monitoring and neuroimaging do not support or refute their usefulness in prognostication (evidence level U).²

Questions for consideration:

1. Is the cortical SEP response normal?
2. What is the patient's prognosis according to the SEP result?
3. What action would you recommend based on this SEP finding?

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Figure Somatosensory evoked potentials 3 days after cardiopulmonary resuscitation

Responses recorded after stimulation of median nerves bilaterally at 3.1 Hz, with a stimulus duration of 0.2 ms to produce a noticeable twitch of the thumb, and averaging of 400 responses. Channels 1 and 2 show the SEP responses elicited from Erb point and the neck, respectively. Channels 3 and 4 show the responses recorded from the cortical scalp electrodes over the ipsilateral and contralateral central regions, respectively (arrows).

SECTION 4

In the cortical channels, an SEP response with a shortened latency of 13 ms seems to be present bilaterally (figure, arrows). Physiologically, a cortical SEP latency of 13 ms after stimulation of the median nerve in an adult is impossible. These responses are volume-conducted from the cervical spinal cord. The results of this test can thus be interpreted as absent cortical SEP responses bilaterally. Bilaterally absent cortical N20 responses have been shown to be strongly associated with a poor prognosis in comatose survivors after cardiopulmonary resuscitation.⁶ Life-sustaining treatment was discontinued based on the clinical picture (persisting deep coma 72 hours after cardiopulmonary resuscitation with no motor response to painful stimuli [evidence level A²] and no confounding effects of hypothermia, hypotension, or sedative medications) and the SEP results. The patient died the next day.

DISCUSSION SEPs are used to determine the function of the somatosensory system. These potentials can be measured at different points of the somatosensory pathways. In the case of the median nerve, the responses can be measured at Erb point, at cervical level (C7), and at cortical level (C3' and C4', 1.5 cm posterior to C3 and C4 according to the International 10–20 System of EEG electrode placement). According to the mean latency measured in milliseconds at different levels, the response at Erb point is called N9, at cervical level N13, and at cortical level N20. In our patient, the measured response at the cortical electrodes could not have been generated in the cortex because there is no time delay compared to the cervical SEP response. It is important to realize that the latency between the cervical and cortical response should be at least 4.5 ms.⁷ Thus it can be concluded that the measured “cortical” response is generated at the cervical spinal cord and spreading to the cortical electrodes because of volume conduction.

Bilaterally absent cortical responses of the median nerve SEP on days 1 to 3 of postanoxic coma have a 100% positive predictive value (false-positive rate 0.7%, range 0–3, evidence level B).² This probably also holds true for most patients treated with therapeutic hypothermia, provided the SEP study is done at least 72 hours after resuscitation, after rewarming, and after the effects of sedative medications have worn off.⁸ Because determining the absence of cortical SEPs has the important clinical implication of whether or not life-sustaining treatment support for the patient should be continued, neurologists need to become well-versed in interpreting the results of this test.

It is important to know that SEPs recorded at the perirolandic region need not always represent intact cortical N20 responses. Especially at enhanced sensitivity

settings (of 0.5 to 1 μ V/cm), there is a chance that volume-conducted SEP responses from Erb point or the neck may be misinterpreted as intact cortical responses. Paying attention to the latency differences between the SEPs at various levels will help to avoid misinterpretation.

Another possible misinterpretation is when bilateral N18 responses (believed to be generated in the brainstem) are reported as intact N20 responses.⁹ However, in such cases it is debatable whether the prognosis is as poor as in a patient with no recordable N18 and N20 responses.

One also needs to be aware of the confounding effect of artifacts on interpretation of SEPs. Artifacts due to shivering, tremor, or myoclonic jerks can result in poor signal to noise ratio, making interpretation difficult. Administering a short-acting neuromuscular blocking agent such as rocuronium can help in abolishing these muscle artifacts without influencing the SEPs.

The question remains whether absent cortical SEPs in a patient after cardiopulmonary resuscitation are 100% reliable in predicting poor outcome, because a confounding effect due to self-fulfilling prophecy is difficult to exclude in most studies.⁸ A recent retrospective study identified one patient who had bilaterally absent SEPs on the third day after cardiac arrest but subsequently regained consciousness with normal cognitive functions in a series of 112 patients treated with hypothermia after cardiac arrest.¹⁰ This patient, with a ROSC time of 10 minutes, was receiving midazolam and fentanyl at the time of the SEP study,¹⁰ which may have confounded the interpretation of the results. The SEP studies providing evidence supporting the AAN guidelines² were performed before therapeutic hypothermia had become a standard neuroprotective treatment. Large prospective studies need to be done in such patients to assess the confounding effect of hypothermia on SEPs. Decisions regarding discontinuation of treatment in patients with inconclusive SEP results are best done in a multidisciplinary team with due consideration of the clinical picture and results from multiple modalities of investigations such as neuroimaging and EEG.

AUTHOR CONTRIBUTIONS

S.C. Li drafted the initial manuscript and was involved in the interpretation of the SEP results for patient care. M.T. de Graaf revised the manuscript and was involved in the interpretation of the SEP results for patient care. P.J. Cherian revised the manuscript, created the figure, and was involved in the interpretation of the EEG and SEP results for patient care.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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