Anoxic Encephalopathy

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Introduction

Anoxic encephalopathy, or hypoxic-ischemic brain injury, is a process that begins with the cessation of cerebral blood flow to brain tissue, which most commonly results from poisoning (for example carbon monoxide or drug overdose), vascular injury or insult, or cardiac arrest. Many patients who suffer anoxic brain injury expire without regaining full consciousness, and many patients have significantly poor neurologic outcomes. However, some advances are beginning to demonstrate preservation of brain tissue, and there is a focus on identifying patients with the prospect of improving neurologic morbidity and mortality.[1] There has been published data to indicate that there are predictors for poor outcome. However, evidence of factors suggestive of good prognosis or outcome has lagged. This activity will review the literature and practices concerning anoxic encephalopathy and brain injury.

Etiology

Patients experience anoxic brain injury as a result of decreased oxygen delivery to the various regions of the brain; this may be due to cardiac arrest, where global hypoxia is a common observation or vascular injury or insult where a more localized area may be affected. In the case of post-arrest patients, an increase of body temperature, which may be neurologically mediated, beyond 37 degrees Celsius is associated with less favourable neurologic outcome and appears to also worsen with every degree beyond 37 degrees Celsius.[2]

Epidemiology

Epidemiology as it concerns gender,

age, or race has not been shown to have a predominance, due to the variable outcome from the primary causation leading to anoxic injury. Most commonly, the cause of anoxic injury is due to cardiac arrest and includes either in-hospital cardiac arrest (IHCA) or out-of-hospital cardiac arrest (OHCA). Though surveillance of statistics regarding cardiac arrest and the neurologic outcome is varied, further studies are needed to determine the differences between IHCA and OHCA. The all-cause post-arrest anoxic injury is the most researched etiology at this time.

History and Physical

A thorough history is the most helpful initial aspect but usually must be obtained from several sources. Because patients with anoxic brain injury are typically unresponsive upon initial presentation, sources such as family members, individuals who were part of the initial resuscitation of the patient, or outpatient care providers can provide information regarding the patient's medical history and witnessed events or interventions performed. A full understanding of baseline neurologic status is essential; utilizing the resources that may have known the patient before the event. Information such as prodromal symptoms, medication use, substance abuse, time of onset, and, if applicable, duration of CPR should also be ascertained if possible.

The elimination of confounding factors is also necessary for a reliable neurologic examination. These factors include, but are not limited to, sedating medications, anticholinergic medications, paralytic drugs, metabolic abnormalities such as acute hepatic or renal failure, shock or continued irreversible hypoperfusion state, therapeutic hypothermia from targeted temperature management and pathologic hypothermia. These conditions have a potential impact on cerebral consciousness as well as reflexes of the brainstem and do have the possibility to demonstrate false findings on detailed neurologic examination. Particularly on the initial evaluation of the patient, these considerations are paramount and should be actively pursued when considering the neurologic examination of an obtunded patient.

There may be physical findings of myoclonic activity or myoclonic status epilepticus in the setting of anoxic encephalopathy. While this may produce confounding examination findings, this does not exclude anoxic

injury. Findings of post-hypoxic myoclonus may be observed usually within 24 hours after hypoxic insult has occurred. However, there are case reports available that describe delayed myoclonus even 48 hours after hypoxic insult due to sedation or paralytic medication use.[3] One factor to consider is that post-hypoxic myoclonus is typically generalized and does not demonstrate particular focality.[4]

Evaluation

In the evaluation of suspected anoxic injury, there should always be a thorough investigation of confounding metabolic abnormalities. Testing performed should include a comprehensive metabolic workup including serum electrolytes, hepatic studies including ammonia, blood gas analysis for acid-base disturbances, as well as hemoglobin measurement, to ensure adequate delivery capacity for oxygen. Potential causes such as infection or drug overdose should be considered as well using cultures and drug and toxicology screens, respectively. If the precipitating event was cardiac arrest, a cardiac evaluation, including echocardiogram and cardiac biomarkers, could be considered. Discussing a further toxicology or cardiology evaluation with the team is essential.

Computed tomography (CT) imaging of the brain is typically performed, which may demonstrate acute findings of subarachnoid or intracranial hemorrhage as the source of the patient's decreased level of consciousness. In cases without intracerebral hemorrhage where there is cardiac arrest related hypoxic injury, initial CT imaging of the brain is frequently normal. However, repeat CT imaging is recommended by post-arrest day three as this will often show manifestations of anoxic injury such as cerebral edema and/or inversion of gray-white matter density.[5] Magnetic resonance imaging (MRI) has also been shown to play a role in the diagnosis of anoxic injury using diffusion-weighted MRI.[6] For the concern of global anoxic injury resulting in brain death, nuclear medicine cerebral diffusion study can be considered to evaluate for cerebral blood flow.

The utility of electroencephalogram (EEG) is somewhat unclear in the routine diagnosis of anoxic encephalopathy due to the potential for interpretation variability due to sedation or drug use, metabolic abnormalities, or sepsis. There are specific findings that may suggest the presence of anoxic injury. However, the extent remains unclear.

These findings include alpha-theta pattern, intermittent or continuous seizures, burst-suppression, generalized periodic complexes, complete or near complete suppression, as well as generalized or focal low voltage output.[7,8] Knowing the limitations, there are EEG classification systems for anoxic encephalopathy that have been proposed. One system classifies the encephalopathy into four different grades utilizing global waveform patterns seen on EEG. Grade I anoxic encephalopathy has the most favorable prognosis and consists of alpha wave activity. Grade II anoxic encephalopathy consists of predominantly theta wave activity on EEG. For grade III, a predominant delta wave pattern is typical, and this extends into grade IV, where the low amplitude delta waves approach an isoelectric EEG.[9] A delta wave pattern is associated with a worse prognosis, and the isoelectric EEG is suggestive of a poor outcome. In order to fully evaluate these findings, monitoring using continuous EEG is preferred to single static EEG. Continuous EEG with therapeutic hypothermia can also be performed, and malignant changes observed during re-warming are associated with poor prognosis.[7]

Treatment / Management

The initial course of management is stabilization of the patient upon presentation; this includes correction of metabolic abnormalities, initiation of antibiotics if septic, stabilization of hemodynamics, as well as a reversal of any possible toxic ingestions or overdose. Potential interventions regarding anoxic encephalopathy include post-arrest targeted temperature management as well as management of seizures should they present. It is also essential to commence discussion with family members regarding the potential for anoxic insult in preparation for permanent neurological damage or death.

Targeted temperature management is the process of maintaining the temperature at or below 36 degrees Celsius, whereas therapeutic hypothermia involves maintaining the temperature within the range of 32 to 34 degrees Celsius. Historically, the suggested temperature range was 32 to 34 degrees Celsius,[10] however, newer trials suggest similar benefit at 36 degrees when compared to 33 degrees giving rise to targeted temperature management.[11] While temperature management may be accomplished using external cooling, therapeutic hypothermia may require

the use of invasive cooling measures.

The indication for temperature management is any patient who, after cardiac arrest, does not demonstrate purposeful movements or follow commands. Both therapeutic hypothermia and temperature management can also be useful in patients undergoing coronary catheterization or receiving thrombolytic medications, as well as patients who are pregnant; however, there is an increased risk of bleeding in these populations.[12] Therapeutic hypothermia is not a recommendation in patients with active non-compressible bleeding; however, targeted temperature management is an option.

Initiation of temperature management is suggested after initial resuscitation in individuals who have non-purposeful motor responses, no evidence of cerebral edema on CT imaging, and, if available immediately, no malignant features on EEG. The duration should be at least 24 hours, although there are studies that demonstrate a slight advantage to 48 hours, albeit with a higher risk of adverse effects.[13] Therapeutic hypothermia should be a possible therapy in patients who, after initial resuscitation, demonstrate CT imaging evidence for the development of cerebral edema, lack motor function or brainstem reflexes, or have malignant EEG patterns if available. The recommended duration is consistent with temperature management.

In both targeted temperature management and therapeutic hypothermia, shivering may cause a delay in obtaining temperature goals. Sedation may suppress the shivering response. However, neuromuscular blockade may ultimately be required. Neuromuscular blockade may mask the physical manifestations of seizures, and it is recommended that the use of neuromuscular blockade should be in conjunction with continuous EEG monitoring.[14,15]

After meeting the therapeutic hypothermia timeframe, the rewarming portion of intervention begins. If automated devices controlling either intravascular or surface cooling are implemented, changes in temperature can undergo adjustment for specific targets. Rates of warming should not exceed 0.5 degrees Celsius per hour. The recommendation is actually that the rate is maintained at 0.25 degrees Celsius per hour instead.[16] If automated devices are not in use, manual rewarming is an option. Changing temperature on cooling blankets or gradually removing ice packs are examples of

manual rewarming. The goal rate of rewarming is 0.5 degrees Celsius every three hours, and monitoring is by checking core temperature.

Differential Diagnosis

When considering a diagnosis of anoxic encephalopathy, examination and observation are required to ensure no confounding factors contribute to the current neurologic presentation. Therefore, metabolic abnormalities such as hypernatremia, hyponatremia, and hypoglycemia, among others, must be considered and corrected prior to diagnosis of anoxic encephalopathy. Sepsis also merits consideration. Drug overdose or alcohol intoxication can also present with neurologic findings that may mimic anoxic injury. Use of sedation medication or neuromuscular blocking agents will also demonstrate neurologic findings and deficits that may be mistaken for anoxic injury.

Anoxic encephalopathy and neurologic injury can also have various presentations. Anoxic injury can present as an initial comatose state, where self-awareness and sleep-wake cycles are absent. Typically, in two to four weeks, a comatose patient will either show some recovery or may progress to a persistent vegetative state or brain death. The persistent vegetative state (PVS) lacks self-awareness, but it does maintain the sleep-wake cycle.[17] PVS does require meeting a set of diagnostic criteria for formal diagnosis from numerous repeat neurologic examinations.[18] If the requirements are not completely satisfied, the term minimally conscious state is used to describe the current neurological condition.[19]

Locked-in syndrome is a state where self-awareness is likely to present in addition to the preservation of the sleep-wake cycle. Typically this will result in persistent quadriplegia, although it does have the potential for prolonged survivability. Akinetic mutism is a condition where damage to the frontal lobe of the brain results in lack of movement or speech initiation, is also a potential condition that may be the result of anoxic injury among other causes. Dementia, particularly advanced dementia, should also be considered especially with a known history.[17]

A physical feature that may be present is post-hypoxic myoclonus.[3,4,3] While this is suggestive of hypoxic insult likely from anoxic injury, consideration of status epilepticus or other seizure

activity is warranted. Evaluation with continuous EEG is ideal if available. A bispectral index can also be utilized; it is more limited in terms of surveillance of multiple regions of the brain. In addition to seizure disorders, the Lance-Adams syndrome also correlates with myoclonus but a favorable neurologic outcome. Neurology consultation may help to distinguish post-hypoxic myoclonus from Lance-Adams syndrome.

Prognosis

Prognosis is often a paramount question that providers will handle routinely in the setting of anoxic encephalopathy. However, studies regarding accurate prognosis have yet to validate a solitary evaluation or scoring system. Currently, several scoring systems based on imaging, testing, and exam findings exist and may be of more benefit in discussions of current neurologic status and potential outcome with families. Factors such as shorter time to initiation of CPR, shorter duration of CPR, and ventricular tachycardia or ventricular fibrillation as the identified arrest rhythm are associated with improved outcome. However, the evaluation and findings of the provider are still the choices over scoring systems for routine practice.

Several scoring systems that attempt to predict prognosis relates to post-arrest anoxic encephalopathy. The GO-FAR score is a tool that retrospectively analyzed in-hospital cardiac arrest patients and predicted the likelihood of survival with good neurologic outcome based upon 13 clinical variables.[20] According to the study, the scoring system drafted may have utility in predicting a low or very low likelihood of survival with good neurologic outcome after in-hospital cardiac arrest and may aid in the discussions of advance directives with the family.

The prognosis after resuscitation (PAR) score is another post-arrest score that aims to predict survival; it also was a retrospective analysis of in-hospital cardiac arrest patients.[21] It also may serve a role in advance directive discussion with families, however, has not been validated for routine use for clinical decision-making.

The brain arrest neurological outcome scale (BrANOS) was formulated using retrospective data that incorporates radiologic findings into prognosis in addition to Glasgow coma scale and duration of cardiac arrest. Combining these data, the prognosis of severe

neurologic disability and mortality were estimated up to 90% accuracy.[22] However, these data did not include patients who underwent therapeutic hypothermia, and therefore, this scale has not yet been fully validated and is not recommended for routine use.

In addition to prognostic scales, there is a physical test that can provide prognostic information using stimulation of the median nerve bilaterally. This testing evaluates for somatosensory evoked potentials (SSEP), which are averaged electrical responses in the central nervous system to somatosensory stimulation peripherally to remove the possibility of peripheral nervous system damage confounding exam findings. This testing does require expert consultation for implementation and interpretation. SSEP evaluation aims to evaluate for the presence of N20 response from the primary somatosensory cortex bilaterally. [23] If absent bilaterally within the first week, often tested 24 to 72 hours post-arrest, it is likely there will be no outcome better than a persistent vegetative state.[24] In addition, SSEP testing has also demonstrated to be the least susceptible testing to metabolic change as well as drugs.[23] If the N20 response is present upon initial testing, consideration to test a second time should be given after the first week has passed as the N20 response may extinguish at that time.

Ultimately the area of predicting prognosis continues to develop, and at this time there is no fully validated prognostic scale. However, the combination of initial testing continued neurologic evaluation, and ancillary testing can provide information regarding the likelihood and can assist surrogate decision-makers in determining the extent of treatment.

Complications

The complications of anoxic encepha-lopathy most commonly present as seizures, myoclonus, or permanent disability. Other complications may be due to inability to effectively treat, such as difficulty maintaining temperature management or therapeutic hypothermia, or iatrogenic, such as rapid rewarming, infusion of excessive crystalloid causing metabolic abnormalities or edema.

Therapeutic hypothermia is known to cause changes in coagulation and hemostasis; therefore, there is a risk of bleeding due to not only decreased platelet function but also decrease coagulation factor activity.[25,26] Rarely does this cause significant bleeding to

alter hemodynamics; however, if present therapeutic hypothermia should be abandoned in favor of temperature management. Therapeutic hypothermia has also been shown to cause bradycardia. However, this is often transient and is often acceptable with normal blood pressure.[27] Drug metabolism is also impacted by therapeutic hypothermia, and this may delay the metabolism of drugs that could cause physical exam changes.[28]

In contrast, rapid rewarming can occur with inadequate monitoring of temperature, particularly a core temperature. The consequences of rapid rewarming include seizures, cerebral edema, and electrolyte disturbances, in particular, hyperkalemia. The ideal core temperature monitor is with the use of a central venous probe. However, surrogate temperature monitoring is available by the use of esophageal, rectal, or bladder probes.[29] The esophageal probe is thought to be the most reliable surrogate for temperature monitoring.

Deterrence and Patient Education

The focus of education is routinely the education of family members or surrogate decision makers. Early summarization of events leading to the current presentation as well as the likelihood of survival with good neurologic outcome and prognosis is essential. Because of involuntary reflexes that may appear as crying, facial grimacing, or other expressions of suffering, explanation of the lack of consciousness and suffering in a coma can provide relief. Discussion of prognosis early, with reinforcement and updates regarding clinical findings, can greatly aid surrogate decision-makers in consideration of goals of care and re-evaluation of whether the current care regimen is consistent with the patient's values and goals.

Enhancing Healthcare Team Outcomes

The management and care of patients with suspected anoxic encephalopathy or anoxic injury are challenging and should involve individuals from not only medical teams but also supportive roles. This includes an interprofessional team approach including care management, nursing, pharmacy staff, dieticians, palliative care, and neurology consultation. Daily collaboration as a team to discuss further management and findings to inform surrogate decision makers is essential and may best be

performed as a collaboration to ensure there are no gaps in information. Pharmacists review medications prescribed, detect drug-drug interactions, and counsel patients and their families. Specialty trained nurses in critical care and neuroscience provide prescribed treatments, monitor patients, educate family members, and give status updates to the team.

The outcomes for patients with anoxic encephalopathy depend on the age of the patient, the extent of brain injury, the presence of neuropsychiatric deficits at the time of diagnosis and comorbidity. For most patients, recovery is prolonged and requires extensive rehabilitation.

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CREDITS: Messina Z, Hays Shapshak A, Mills R. Anoxic Encephalopathy. [Updated 2020 Apr 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/ books/NBK539833/