Pearls & Oy-sters: Eyes-Open Coma

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Pearls

- The classical definition of coma denotes unarousable unresponsiveness with absent sleep–wake cycles and closed eyes, but comatose patients may defy that definition by showing eye-opening early after brain injury.
- Coma with eye-opening (either spontaneously or on physical stimulation) differs from the vegetative state/unresponsive wakefulness syndrome (UWS) in that it has a different clinical trajectory (worsening rather than stabilization) and no sleep–wake cycle.

Oy-sters

- Coma with eye-opening may occur with supratentorial, infratentorial, or global brain insults of various etiologies (e.g., stroke, anoxia). Brainstem involvement either as primary injury or secondary injury due to herniation appears to be a commonality among patients with eyes-open coma.
- International efforts¹ are underway to develop an endotype-based coma definition that considers actionable pathophysiologic information and clinical trajectories (as opposed to a merely descriptive coma phenotype); hence, the classical definition of coma is likely to be modified in the future.

Assessment of eye-opening is key to the evaluation of unresponsive patients. According to the seminal definition by Plum et al.,² coma is a state of profound unawareness from which the patient cannot be aroused, a normal sleep–wake cycle is absent, and the eyes are closed. Classically, return of eye-opening after brain injury is thought to indicate recovery of consciousness or progression to UWS (i.e., wakefulness without clinical signs of awareness).³ However, some comatose patients exhibit eye-opening (either spontaneously or on physical stimulation) early after brain injury and do not meet criteria for UWS. Prognostic scales such as the Glasgow Coma Scale and the Full Outline of Unresponsiveness (FOUR) score,⁴ which both positively weight spontaneous eye opening, may generate overly optimistic outcome estimations for patients with eyes-open coma. Here, we present 3 case vignettes, with infratentorial, supratentorial, and global brain injuries, illustrating an underrecognized coma phenotype that is characterized by spontaneous eye-opening, but poor, and often fatal, outcomes.

Case Vignette 1: Infratentorial Brain Injury

A 62-year-old woman with a history of hypertension and diabetes presented with sudden onset of left hemiparesis and dysarthria (NIH Stroke Scale 6). Head CT showed small right caudate and corona radiata hypodensities that appeared chronic. She received IV tissue plasminogen activator (tPA) within 53 minutes after stroke onset. CT angiogram revealed bilateral vertebral artery intracranial stenosis, but no large vessel occlusion. Thirty-seven minutes after initiation of tPA, the patient complained of a headache and became unresponsive. tPA was stopped, the patient intubated, and cryoprecipitate administered. Repeat head CT demonstrated a 35 mL pontomedullary intracerebral hemorrhage with intraventricular hemorrhage and hydrocephalus. The next day, off

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A. Eye opening with DBS during anesthesia

B. Eye opening with brain death

This figure shows a schematic rendering of 2 previously published cases of eye-opening with deep brain stimulation (DBS) during general anesthesia⁸ and brain death,⁹ highlighting the anatomical pathways related to eye-opening without awareness. Original patient images are available from Moll et al.⁸ and Santamaria et al.⁹ (A) A 42-year-old woman underwent deep brain stimulation for cervical dystonia. Intraoperatively, the patient's eyes were closed without stimulation (left), while electrical stimulation of the internal segment of the globus pallidus internus (GPI) and the adjacent basal nucleus of Meynert (NBM) evoked continuing bilateral opening of the eyelids without awareness (right). Hence, the GPI (1) and NBM send descending inputs through the paramedian tegmentum of the upper brainstem (2) onto the oculomotor nucleus complex (3), from which oculomotor nerve fibers (4) eventually innervate the levator palpebrae muscle (5) on both sides, leading to full eye-opening. (B) A 47-year-old man was declared brain dead following a standard brain death protocol, including documentation of absent intracranial blood flow using nuclear scintigraphy. Nevertheless, painful stimulation of the left nipple (but no other area) consistently induced slow ipsilateral eye-opening. Here, residual sympathetic function of the low cervical/upper thoracic cord (1) is transmitted via the sympathetic trunk and the superior cervical ganglion (2) to the superior division of the oculomotor nerve (3) and eventually the Müller muscle (4), thereby bypassing the brainstem. The eye-opening was unilateral and less pronounced owing to the relative weakness of the Müller muscle. Figure created with biorender.com.

sedation, the patient's eyes were both persistently halfway open, requiring artificial tears to prevent corneal abrasions. She did not obey commands, there was no physical response to verbal stimuli, and she did not fixate, saccade to stimuli, or track. Her gaze was midline and there was no blink to threat. There were no oculocephalic movements or corneal reflexes; her pupils were 6 mm bilaterally and unreactive with a pupillometer, and she was apneic when switched to pressure support ventilator mode. She had a cough with deep suctioning, extended both lower extremities, and had plegic upper extremities with noxious stimuli (FOUR score: eyes 3, motor 1, brainstem 1, respiration 0; total 5). Four days later, she was declared brain dead based on clinical examination and an apnea test.

Case Vignette 2: Supratentorial Brain Injury

A 61-year-old man with a history of hypertension and hypercholesterolemia developed sudden onset of headache, neck stiffness, and vomiting. In the emergency department, the patient was unarousable with a right fixed and dilated pupil and bilateral upper extremity flexor posturing. The patient was intubated. Head CT demonstrated a modified Fisher 4 subarachnoid hemorrhage dissecting into the right subdural space with 17 mm midline shift. CT angiogram revealed an 18 mm right supraclinoid internal carotid artery aneurysm. Upon arrival in the intensive care unit, his examination off sedation revealed spontaneously open eyes, but no blink to threat,

saccade to voice, tracking, or command following. Using a pupillometer, the right pupil was 5 mm and fixed; the left pupil was 3 mm and reactive. Corneal, cough, and oculocephalic reflexes were present and the patient was breathing above the ventilator. He showed bilateral extensor posturing with noxious stimuli (FOUR score: eyes 3, motor 1, brainstem 3, respiration 1; total 8). Based on the patient's known wishes, the patient was transitioned to comfort care and died on postbleed day 4.

Case Vignette 3: Global Anoxic Brain Injury

A 50-year-old patient had out-of-hospital cardiac arrest and return of spontaneous circulation after 20 minutes. The patient was treated with 24 hours of therapeutic hypothermia. CT of the brain showed mild generalized sulcal effacement; neuron-specific enolase was 187/L. EEG the next day revealed a flattened background with monomorphic generalized periodic discharges. The eyes were spontaneously halfway open and fully opened following sternal rub and temporomandibular joint pressure. There was no blink to threat and no visual pursuit or fixation during the mirror test. Automated pupillometry showed minuscule pupillary reactions to light; pupils were pinpoint. Corneal reflexes were absent, as were oculocephalic reflexes. There was preserved cough on tracheal suction including a rise in blood pressure. There were a few myoclonic jerks in the face, occasionally increasing with physical stimulation but unrelated to the generalized periodic discharges,

suggestive of subcortical myoclonus. The FOUR score was eyes 3, motor 0, brainstem 2, respiration 0 (total 5). Median nerve somatosensory evoked potentials on day 3 showed absent N20 responses and CT of the brain revealed generalized edema, including a white cerebellum sign and temporal horn enlargement. The patient was terminally extubated.

Discussion

Each patient presented acutely after brain injury with prolonged eye-opening despite unarousable unawareness. Unlike UWS, which typically develops weeks after coma onset, there was no neurologic improvement or stabilization, such as return of sleep–wake cycles. Instead, brainstem reflexes were progressively lost, including nonreactive pupils, and eye-opening was present until death. Although the FOUR scores ranged from 5 (associated with ~50% in-hospital mortality⁴) to 8 (~30% in-hospital mortality), all 3 patients died in-hospital, including 2 who died following withdrawal of life support owing to their poor neurologic status. The implication of this observation is that comatose states exist that challenge the classic definition of coma,² stressing the importance of recent initiatives like the Neurocritical Care Society’s Curing Coma Campaign, which aims to characterize the anatomical, electrochemical, and electrophysiologic underpinnings of coma and disorders of consciousness.¹

The exact anatomical and physiologic mechanisms in coma with eye-opening are unknown. Normally, elevation of the eyelids involves activation of the levator palpebrae superioris muscles (LPS) and concurrent inhibition of the orbicularis oculi muscles. The LPS receive bilateral innervation from the central caudal nucleus of the oculomotor nucleus complex. The supranuclear control is less well understood. Experimental data suggest involvement of the cortex, extrapyramidal motor systems, and rostral brainstem structures, and some evidence indicates that the right hemisphere may be dominant for cortical eyelid control.⁵ In our patients, coma with eye-opening occurred with a primary infratentorial lesion, a supratentorial lesion with brainstem herniation, and a global anoxic insult. In 2 previous reports, periodic eyelid opening following cardiac arrest was associated with a burst-suppression pattern on EEG,⁶ and eye-opening triggered by flexion of an arm was described as a manifestation of the decerebrate response in a patient with diffuse bilateral hemispheric damage,⁷ but neither of these mechanisms was identified in our patients.

Two other cases of unresponsiveness with eye-opening may delineate the anatomical boundaries within which coma with eye-opening may occur (figure). At the most cranial level, intraoperative stimulation of the globus pallidus internus (GPi) in a woman undergoing deep brain stimulation surgery led to consistent eye-opening, despite complete unresponsiveness (figure, A).⁸ Full opening of both eyes could be induced by stimulation in both hemispheres (implying that descending control to the LPS is exerted bilaterally), but was topographically restricted to sites between the GPi and the posterior part of the

basal nucleus of Meynert. The authors suggested that the subpallidal basal forebrain is involved in the premotor control of eye-opening.⁸ Given that the pathways controlling LPS tonus run in close association with the ascending arousal system through the paramedian tegmentum of the upper brainstem, there must have been a dissociation between these intact pathways and a nonfunctioning arousal system.

At the most distal level, consistent (albeit partial and unilateral) eye-opening has been observed in a remarkable case of brain death (figure, B).⁹ As brainstem function was irreversibly lost, the eyelid opening was interpreted as resulting from preserved sympathetic function of the cervical spinal cord, activating the Müller muscle. Indeed, in a similar case, unilateral stellate block with lidocaine abolished eye-opening on the side of the injection, demonstrating the sympathetic origin of this phenomenon.¹⁰

As autopsy was not performed, we can only speculate about the mechanisms at play in our patients. Cerebral edema and distortion of the GPi and basal nucleus of Meynert might have led to tonic activation of LPS pathways and heightened sympathetic activity leading to activation of the Müller muscle is also plausible. However, we can infer that coma can occur in patients who have eyes open all the time and patients showing eye-opening to a noxious stimulus.

These patient vignettes illustrate that a coma phenotype associated with eye-opening exists and defies classic coma definitions. This phenotype occurs with various etiologies, including primary or secondary infratentorial lesions and global anoxic–ischemic injury. Autopsy and functional imaging studies are needed to reveal the mechanisms behind this phenomenon and epidemiologic studies are needed to determine the prevalence and outcomes associated with eyes-open coma.

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Appendix Authors

Name	Location	Contributions
Daniel Kondziella, MD, PhD	University of Copenhagen, Denmark	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Jennifer Frontera, MD	NYU Grossman School of Medicine	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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