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NARRATIVE REVIEW

Stepwise clinical and diagnostic strategy for coma of unknown origin

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Abstract: Coma represents a critical failure of brain systems regulating arousal and awareness, posing significant diagnostic challenges when its origin is unknown. Accurate and timely diagnosis is essential to identify reversible causes and guide treatment. Here, we propose a comprehensive stepwise diagnostic algorithm integrating clinical examination, electroencephalography, neuroimaging, and laboratory investigations, emphasizing iterative reassessment to inform early decision-making. This approach, grounded in the pathophysiology of coma and current consciousness frameworks, facilitates localization of brain dysfunction and prioritizes detection of treatable etiologies. Emerging neurotechnologies, including advanced MRI and multimodal AI, hold promise for enhancing diagnosis and personalized management. Our framework aims to improve clinical outcomes by promoting systematic, physiology-based evaluation of coma of unknown origin in acute-care settings.

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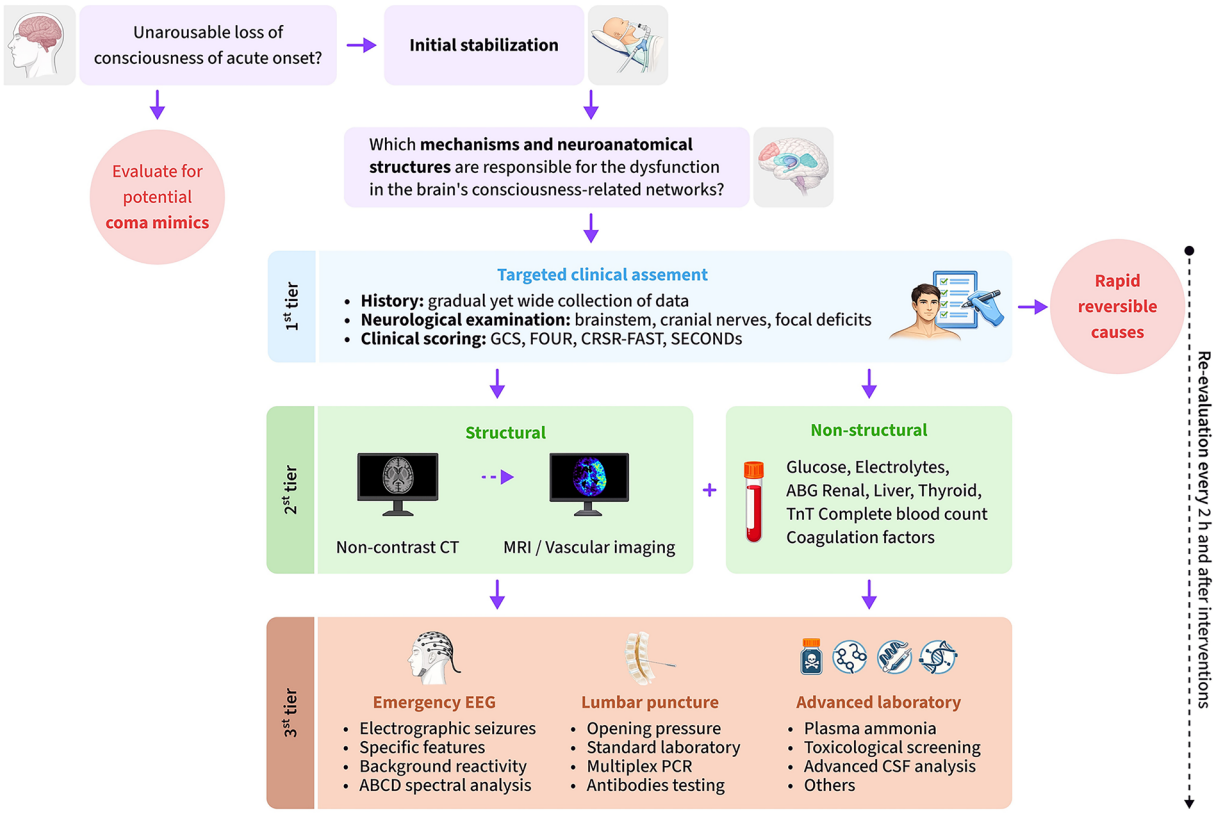
Visual abstract:

STEPWISE CLINICAL AND DIAGNOSTIC STRATEGY FOR COMA OF UNKNOWN ORIGIN

A practical roadmap

Review objectives

- **Present a clear, stepwise diagnostic strategy** integrating bedside examination, EEG, neuroimaging, laboratory tests, and CSF analysis.
- **Focus on early identification of reversible causes** and structured reassessment to guide clinical decisions.
- **Explore emerging tools (advanced MRI, EEG analytics, AI)** that may transform coma diagnosis and management.



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Keywords: Coma pathophysiology, Clinical examination in coma, Neuroimaging in coma, Electroencephalography (EEG), Disorders of consciousness

Introduction

What this review adds

- It proposes a stepwise diagnostic algorithm grounded in coma pathophysiology and the current theoretical framework of consciousness.
- The suggested approach uniquely integrates clinical examination, EEG, neuroimaging, and laboratory findings into a unified diagnostic strategy, which includes structured reassessment loops to guide early and evolving decision-making.
- Dedicated focus on the systematic identification and treatment of reversible causes.
- It provides a forward-looking perspective on emerging neurotechnologies—including covert consciousness detection, advanced MRI, and multimodal AI—that are expected to significantly transform the clinical management of coma.

Coma of undetermined origin remains one of the most diagnostically challenging conditions in acute care, with limited structured guidance on the optimal sequencing of evaluations. The available evidence largely relies on clinical literature describing the presentation and diagnostic priorities of the most common causes of coma [1, 2]. Drawing on recent advances in the neurosciences of consciousness, this review proposes an alternative, step-by-step diagnostic approach aiming at the early evaluation of this complex clinical condition. Indeed, without a systematic diagnostic approach, physicians may perform numerous tests that are either unnecessary or falsely reassuring [3].

When encountering a patient with coma, the clinician must have a structured implemented approach to rapidly identify remediable causes, prevent secondary brain injury, and determine an organized plan for clinically based laboratory, electrophysiological and neuroimaging tests. Prognosis is closely linked to the patient's stabilization and timely treatment of underlying causes, and any delay in their recognition may result in excess morbidity and mortality [2, 4, 5]. In the absence of an obvious cause (i.e., traumatic brain injury, severe stroke, or cardiac arrest), a broad spectrum of disorders may underlie coma origin. Diagnostic efforts are often complicated by limited witness accounts/medical history, and the confounding effects of sedative or intoxicant exposure. The approach is inherently multidisciplinary, involving intensivists, neurologists, physiologists, biologists, and radiologists.

Grounded in the fundamental principles of coma pathophysiology, integrating an understanding of reversible causes, the proposed diagnostic algorithm crucially emphasizes iterative reassessment cycles to shape early and dynamic clinical decision-making. An altered level of consciousness encompasses a spectrum of clinical presentations, ranging from mild confusion to coma, with multiple potential etiologies requiring systematic evaluation. For clarity, the present review focuses exclusively on the most severe end of this spectrum, specifically patients with coma, with absent awareness and responsiveness. Moreover, this review excludes coma related to major traumatic brain injury, hypoxic brain injury after cardiac arrest and large-vessel ischemic strokes, which follow distinct pathophysiological mechanisms and established management pathways, and have been extensively reviewed elsewhere [6–10].

We believe that the proposed framework has the potential to shift the field from a predominantly phenotypic perspective—focused on identifying clinical syndromes—toward a more promising early characterization of targetable coma endotypes, defined by measurable pathophysiological traits [11].

Take-home message

A structured and time-sensitive diagnostic sequence is essential for evaluating coma of unknown origin, beginning with stabilization and rapid identification of reversible causes

The neurological examination remains the cornerstone of early localization, integrating brainstem reflexes, motor patterns, and respiratory clues to guide targeted investigations

CT is the first-line neuroimaging modality, but a normal CT does not exclude serious aetiologies; **MRI provides superior sensitivity** for brainstem, cortical, and diffuse axonal injuries

EEG should be obtained early in all unexplained comas, both to detect nonconvulsive seizures and to assess thalamocortical network integrity through background reactivity and graded EEG patterns

A stepwise laboratory and CSF strategy—prioritizing metabolic emergencies, ammonia, endocrine abnormalities, toxicology, and early CSF evaluation when safe—is critical for diagnosing treatable conditions

Reassessment at regular intervals is mandatory, as coma is a dynamic condition and clinical course may change rapidly following interventions. Initial reassessment should be frequent, often every 15–30 min in the first hours. Once stable, assessment intervals can be extended to every 2–4 h at clinical discretion

Mechanistic insights into frontoparietal and thalamocortical network dysfunction increasingly inform clinical interpretation of EEG and neuroimaging and may refine prognostic accuracy

Emerging technologies including advanced MRI, continuous EEG analytics, CMD detection, pervasive sensing monitoring, and multimodal AI—may transform coma assessment and enable precision neurocritical care

Pathophysiological underpinnings

Coma is a pathological transient state of unarousable loss of consciousness, typically of a sudden onset following

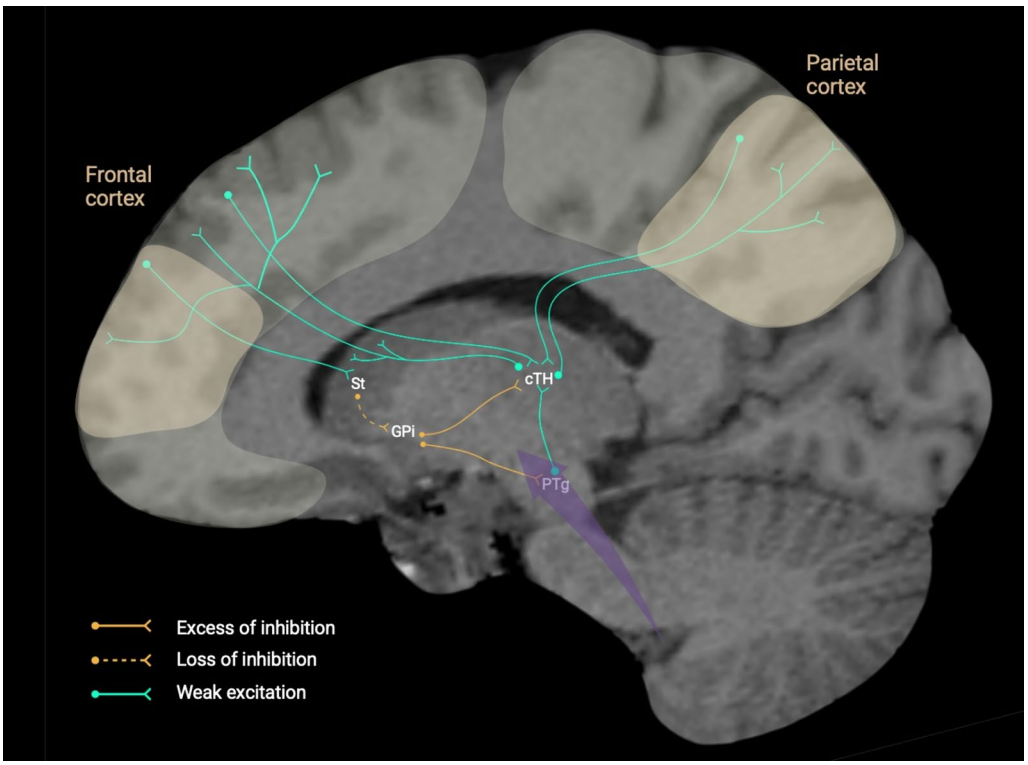

Fig. 1 Representation of the mesocircuit frontoparietal model. In normal conditions, excitatory thalamocortical projections drive cortical activity from the frontal cortex, which in turn activates the striatum (St), as part of the striatal-thalamocortical loop. Striatal output exerts inhibitory control over the globus pallidus interna (GPi), resulting in disinhibition of the thalamus, and facilitation of cortical activation. In disorders of consciousness, striatal underactivation, due to reduced excitation from the frontal cortex, can lead to excessive GPi output, thereby increasing inhibition of the central thalamus (cTH) and reducing thalamocortical outflow to the frontoparietal cortices (in yellow). PTg: pedunculopontine tegmental nucleus. ARAS: ascending reticular activating system (magenta arrow). Hence, following a brain injury, coma can result from (i) focal bilateral lesions within the mesocircuit (bilateral thalamic, pallidal or striatal lesions as well as lesion of the ponto-mesencephalic reticular formation) or (ii) diffuse cortical–subcortical injury

a severe brain injury, that was first defined by Plum and Posner more than 50 years ago[12]. It arises from widespread functional disruption of the neural systems that regulate consciousness, principally the ascending reticular activating system (ARAS) in the brainstem, along with thalamocortical and corticocortical projections, leading to a global decrease in excitatory synaptic activity within the cortex.

Consciousness is commonly conceptualized along two main dimensions: *arousal*, the level of wakefulness, and *awareness*, the content of conscious experience [12, 13]. In this dichotomous model, coma entails a complete absence of arousal, whether spontaneous or stimuli-induced, and a concomitant absence of awareness (internal and external). Following a period of coma, some patients may regain arousal without recovery of awareness, a condition termed the vegetative state/unresponsive wakefulness syndrome (VS/UWS). The subsequent re-emergence of reproducible purposeful behaviors indicates partial recovery of awareness and defines the minimally conscious state (MCS) (for a comprehensive review, see [14]).

From a neuroanatomical perspective (Fig. 1), arousal is mediated by the ARAS, composed of heterogeneous cholinergic, monoaminergic, and glutamatergic neurons within the brainstem that project to the thalamus, hypothalamus, and basal forebrain, which in turn modulate cortical excitability [15]. Destructive lesions within these brainstem structures, such as in pontine hemorrhages or diffuse axonal injury, can lead to coma by interrupting these arousal pathways. The ARAS is thus essential for sustaining arousal and providing baseline physiological conditions necessary for the emergence of awareness [16]. Awareness itself depends on preserved cortical function and its white matter connections with subcortical structures, notably the central thalamus [16]. Extensive cortical dysfunction, particularly in the frontoparietal associative areas, or bilateral thalamic damage disturbs sensory integration and higher order cognitive functions, leading to altered awareness [17].

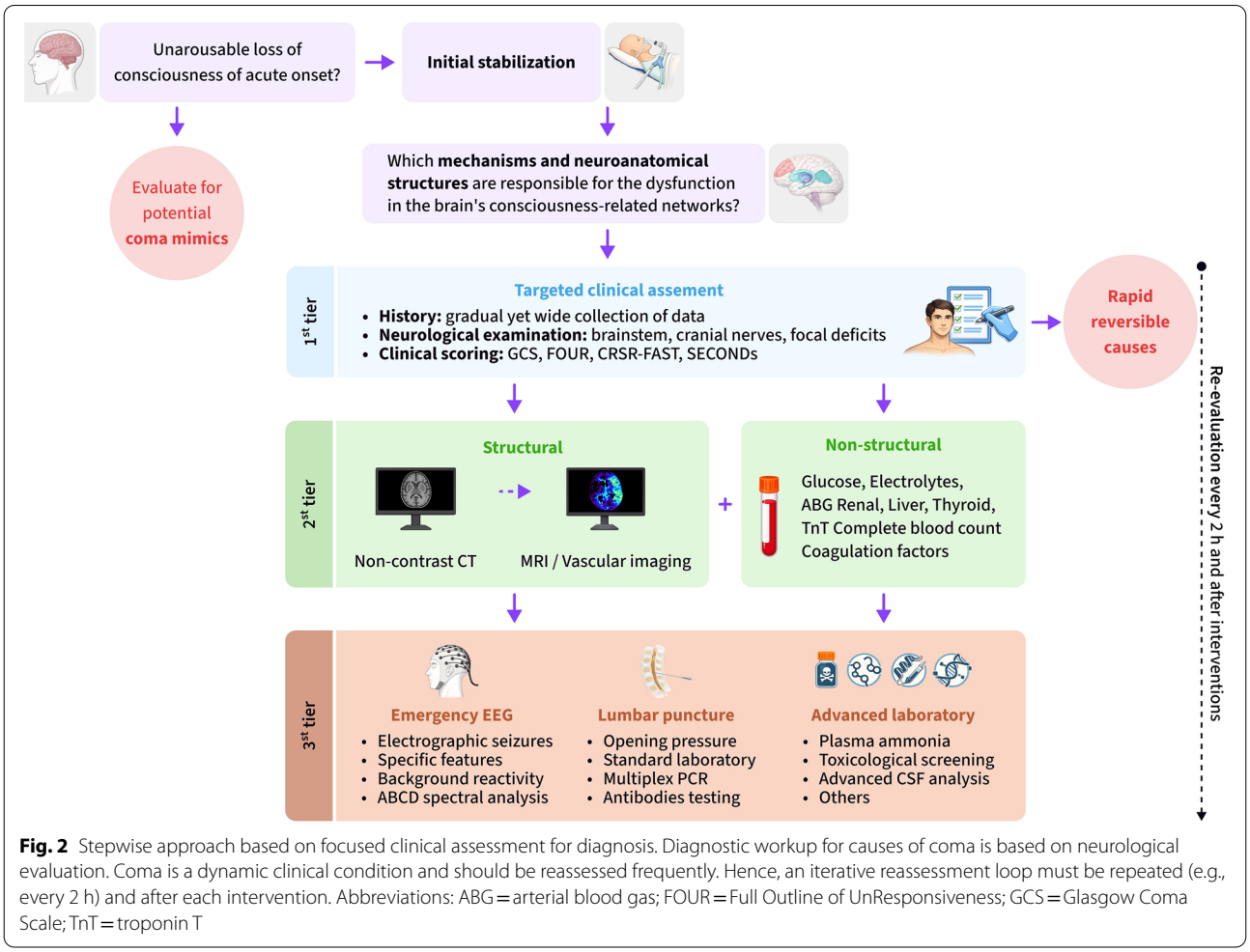

Fig. 2 Stepwise approach based on focused clinical assessment for diagnosis. Diagnostic workup for causes of coma is based on neurological evaluation. Coma is a dynamic clinical condition and should be reassessed frequently. Hence, an iterative reassessment loop must be repeated (e.g., every 2 h) and after each intervention. Abbreviations: ABG = arterial blood gas; FOUR = Full Outline of UnResponsiveness; GCS = Glasgow Coma Scale; TnT = troponin T

Over the past 2 decades, advances in functional neuroimaging have demonstrated that coma is associated with widespread cortical hypometabolism, reduced network connectivity, and disruption of thalamocortical loops. In particular, both the frontoparietal networks and the anterior forebrain mesocircuit appear to be consistently disturbed in coma, while their integrity is linked to recovery [18–23]. It is worth noting that the anterior forebrain mesocircuit is based on the central role of the thalamus—particularly the intralaminar nuclei and its connections to the striatum and the frontal cortex. Within this cortico-striatal-thalamic-cortical loop, direct or indirect damage to the striatum—direct or secondary—might reinforce the inhibitory output from the internal globus pallidus to the thalamus, further affecting the thalamocortical outflow, including to the frontal regions[17] (Fig. 1). As a promising lead for coma clinical management, restoration of mesocircuit function, particularly reactivation of the central thalamus and its cortical projections using pharmacological agents (e.g., zolpidem, amantadine, apomorphine) [5, 24], is associated with neurological recovery in patients with prolonged disorders of consciousness (VS/UWS, MCS).

Overall, coma results either from diffuse, potentially reversible dysfunction of arousal and awareness networks or from direct structural damage to these systems. Metabolic derangements, electrolyte abnormalities, intoxications, and sepsis typically impair consciousness by globally depressing neuronal excitability and synaptic transmission across the cortex and subcortical structures. In these conditions, the ARAS and the fronto-parietal-thalamic mesocircuit are usually anatomically intact but functionally suppressed, leading to reduced arousal and impaired integration of information without focal brain destruction. Additionally, these brain regions may exhibit structural alterations, secondary to common systemic insults observed in the critically ill, including hypoxia, hypoglycemia, and cerebral blood flow alterations. In contrast, coma of neurological etiology arises from direct structural injury to key components of consciousness networks. Destructive lesions affecting the ARAS

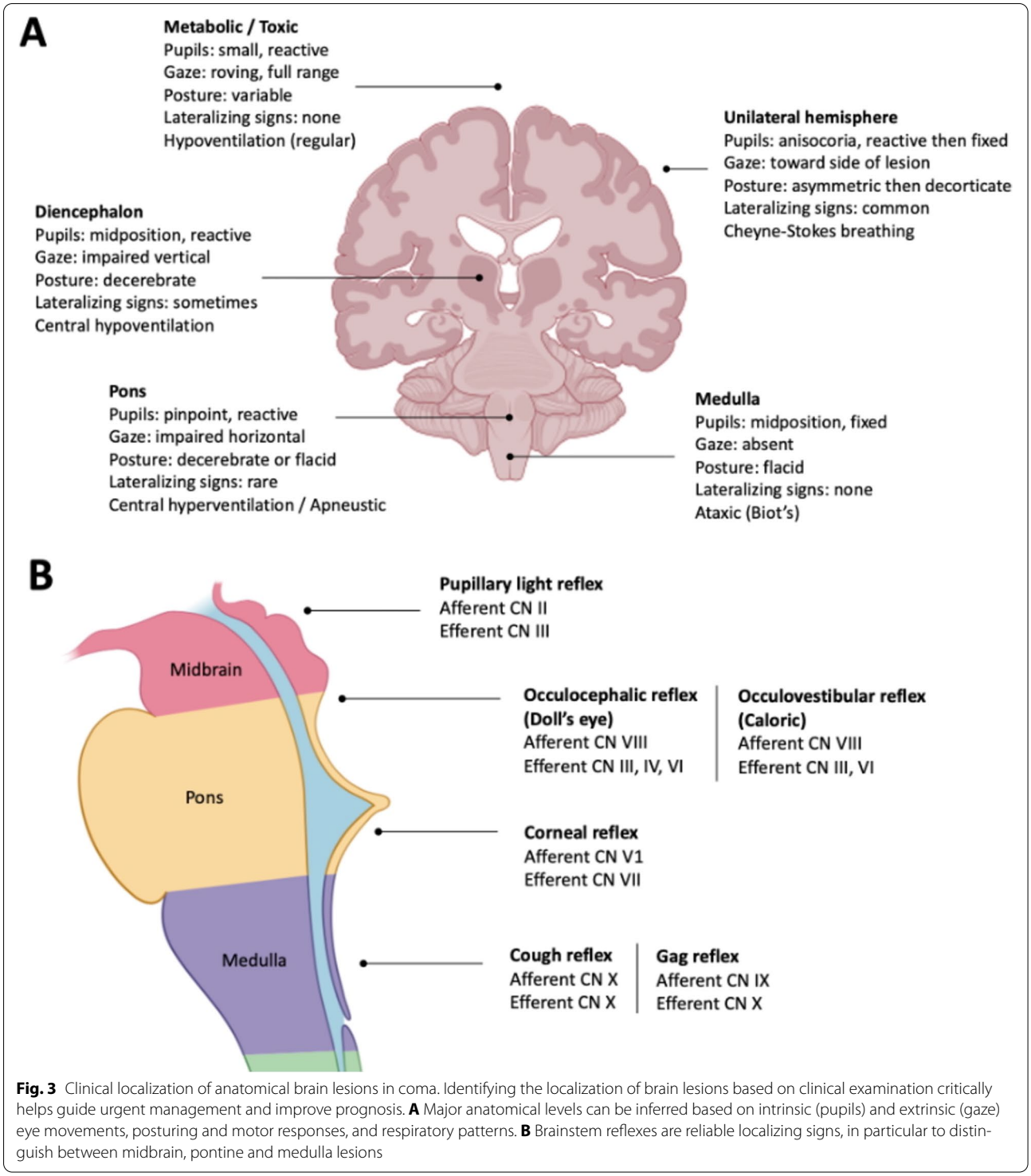

Fig. 3 Clinical localization of anatomical brain lesions in coma. Identifying the localization of brain lesions based on clinical examination critically helps guide urgent management and improve prognosis. **A** Major anatomical levels can be inferred based on intrinsic (pupils) and extrinsic (gaze) eye movements, posturing and motor responses, and respiratory patterns. **B** Brainstem reflexes are reliable localizing signs, in particular to distinguish between midbrain, pontine and medulla lesions

(e.g., pontine hemorrhage, diffuse axonal injury) interrupt arousal pathways, while bilateral thalamic lesions or extensive damage to frontoparietal associative cortices and their white matter connections disrupt awareness by disconnecting cortical integration hubs. Thus, whereas systemic causes produce a functional shutdown of the frontoparietal mesocircuit, structural brain lesions result in anatomical disconnection or destruction, often conferring a worse prognosis and reduced reversibility.

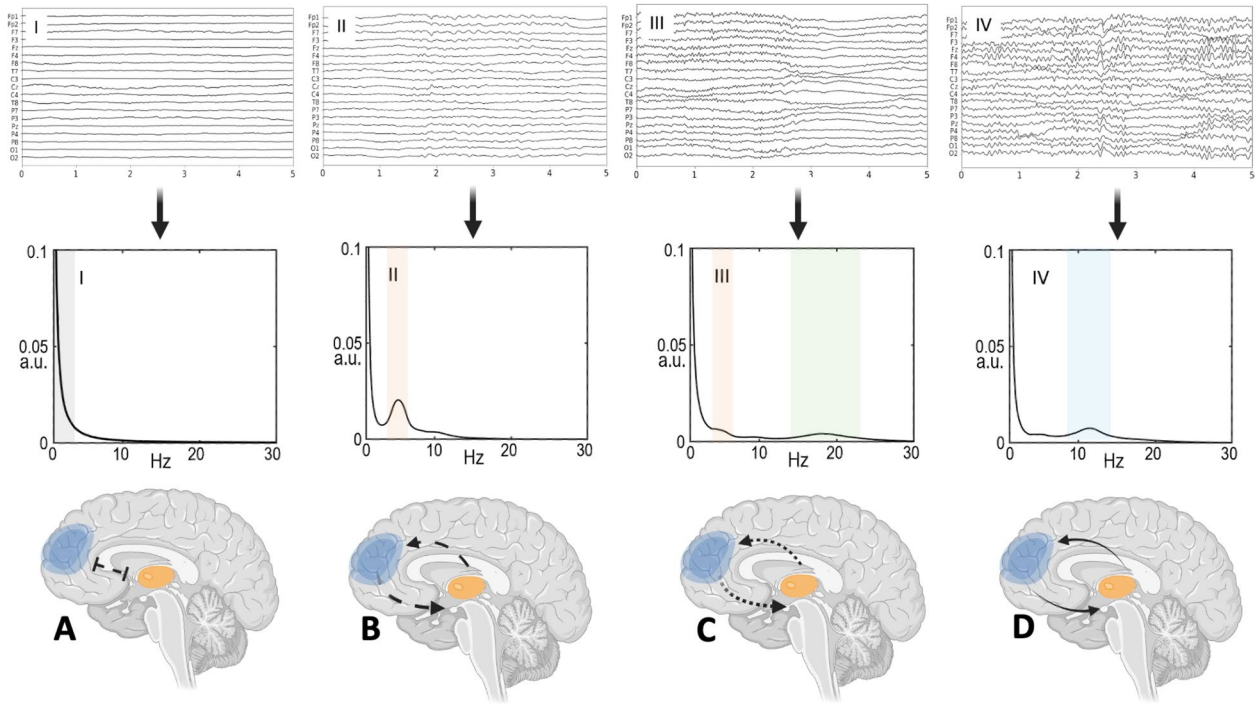

Fig. 4 Sample EEGs and power spectra of commonly observed patterns in comatose patients. Four sample EEGs from patients with coma suggest a graded impairment of the thalamocortical circuit. (I) Suppressed background dominated by delta oscillations (< 4 Hz, highlighted in gray), consistent with complete corticothalamic deafferentation (pattern A); (II) theta activity (5–7 Hz, highlighted in orange), suggesting reduced corticothalamic afferentation (pattern B); (III) mixed theta and beta (~ 15–40 Hz, highlighted in green) activity, possibly reflecting partial reafferentation of corticothalamic systems (pattern C); (IV) broadband alpha (8–12 Hz, highlighted in blue) extending to beta activity, representing normal tonic thalamic firing and resting cortical oscillations (pattern D). a.u. arbitrary units

Clinical implications of the pathophysiology

- Dysfunction of the brain mesocircuit and frontoparietal networks represents a key mechanism underlying coma, with impaired thalamostriatal and thalamocortical connectivity leading to the observed sudden loss of arousal and awareness (Fig. 1). Although the neural substrates of human consciousness have not yet been fully elucidated[3, 18], it is increasingly recognized that all causes of coma—regardless of their origin—ultimately converge on disruption of information flow within these critical brain networks.
- This conceptual framework is clinically relevant for etiological diagnosis, as coma may result from either focal injuries (e.g., involving the ARAS or bilateral thalamic damage) or diffuse cortical injuries affecting these networks, underscoring the diagnostic value of repeated and structured clinical assessments with a specific focus on the identification of localization signs (Figs. 2 and 3).
- Valuable insights into critical thalamocortical disconnection can be obtained directly at the patient's bedside using the ABCD EEG classification, as detailed later (Fig. 4).
- Converging evidence suggests that advanced neuroimaging techniques can be leveraged to evaluate the structural (Fig. 5), functional [19, 25], and metabolic [26, 27] integrity of these networks for coma neuroprognostication, potentially paving the way for future, individually tailored, mechanism-based therapeutic interventions.

Targeted clinical assessment

New-onset coma demands a rapid, efficient and structured evaluation [2]. Despite a growing reliance on neuroimaging and biomarkers, the structured neurological examination remains essential for bedside localization, diagnostic triage, and early prognostication. The algorithm presented in Fig. 2 supports clinicians in acute-care settings by outlining a stepwise approach for the initial evaluation of coma incorporating reassessments as the clinical picture evolves.

Coma of unknown origin requires a "diagnostic detective" approach [28]. Coma mimics (e-Table 1) such as

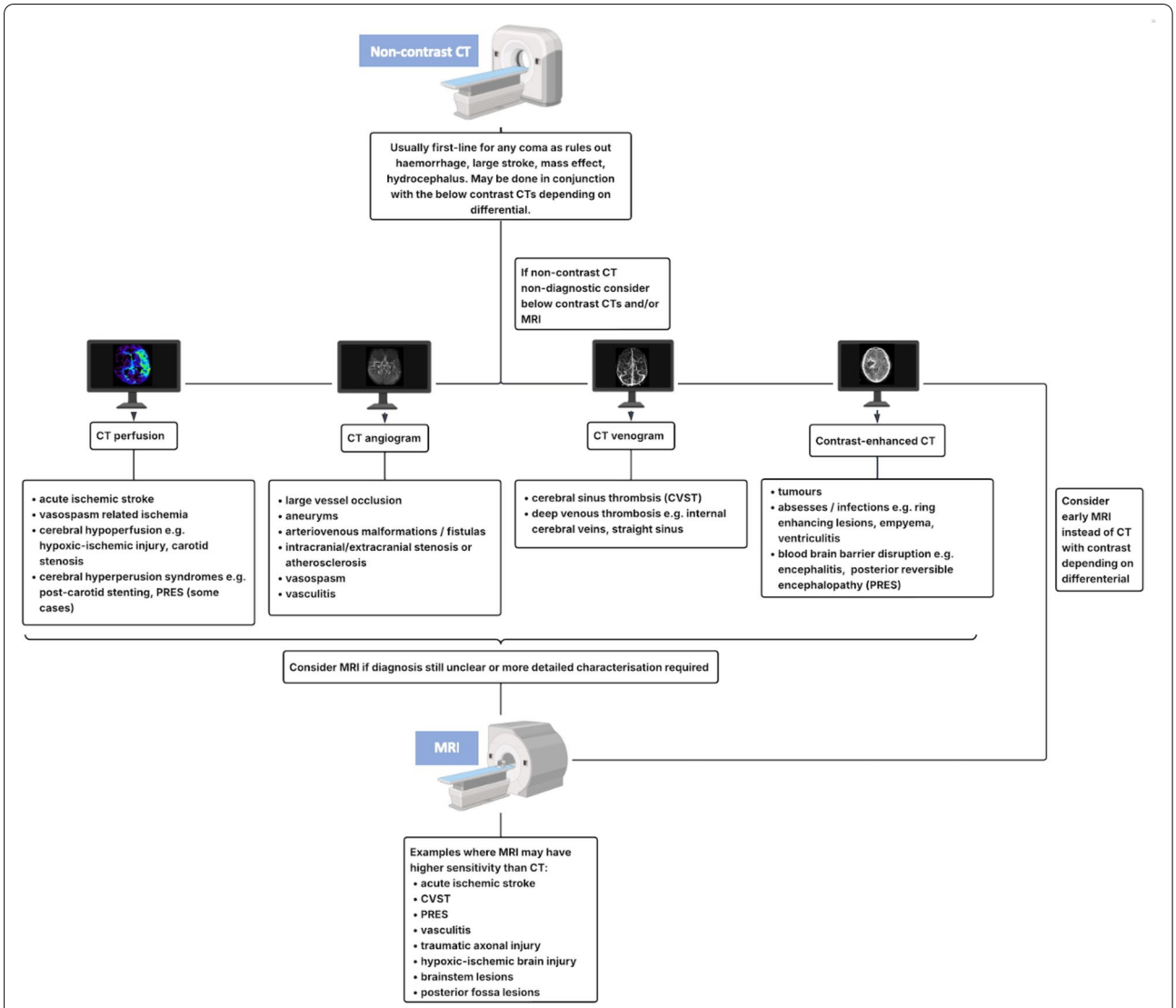

Fig. 5 Diagnosis of coma etiology using conventional neuroimaging. Conventional neuroimaging, specifically computed tomography (CT) and magnetic resonance imaging (MRI), is a cornerstone in diagnosing the causes of coma by rapidly identifying or excluding structural causes. Interpretation of neuroimaging must be integrated with clinical findings, as normal imaging does not exclude several etiologies. Abbreviations: CVST = cerebral venous sinus thrombosis; PRES = posterior reversible encephalopathy syndrome

catatonia, locked-in syndrome, or psychogenic unresponsiveness should also be ruled out with bedside maneuvers and imaging [1]. Moreover, confounders that may mask consciousness should be identified and mitigated [11]. Indeed, sedation, analgesic, body temperature and metabolic disturbances may transiently obscure awareness, thereby creating diagnostic uncertainty. After initial stabilization, clinicians should prioritize excluding non-structural causes that require prompt therapeutic intervention (Table 1) [1, 28, 29]. In all cases, repeated clinical assessments should be carried out whenever possible without sedation and should employ structured consciousness scoring tools (see below for details) [12, 30]. Indeed, sedative and analgesic agents may constitute significant confounding factors within the diagnostic workup of coma, underscoring the importance of closely monitoring sedation depth and limiting both dose and duration to the minimal effective level [31].

All new information should be integrated into the data collected from previous evaluations, taking into account the potential for evolution. Indeed, coma and response to treatment are dynamic processes, and repeated neurological examinations should be performed systematically on a regular basis, and after any intervention. A

Table 1 Reversible causes of coma. They include metabolic, toxic, infectious and certain structural etiologies for which prompt recognition and intervention can restore conscious state. Early identification and targeted treatment of these conditions are mandatory to prevent irreversible brain damage and optimize outcomes

Causes	Required intervention
Dysglycemia	• Hypoglycemia. Intravenous glucose administration (25 gr of 50% Dextrose). Glucagon via intramuscular or subcutaneous if intravenous access is not immediately available • Hyperglycemia. Intravenous fluid resuscitation, electrolyte correction and continuous intravenous insulin infusion
Wernicke's encephalopathy (thiamine deficit)	Parenteral thiamine administration (500 mg intravenous three times daily), especially in malnourished or alcoholic patients
Electrolyte disturbances	Rapid correction of severe hyponatremia, hypernatremia, or other critical electrolyte imbalances
Hypoxia/hypercapnia	Airway management and correction of respiratory failure
Poisoning/drug intoxication	• Opioids. Naloxone (0.4–1 mg inhaled or intravenous) • Benzodiazepines. Flumazenil (0.1 mg/min intravenous) • Carbon monoxide. High flow oxygen or hyperbaric oxygen therapy
Seizures (either convulsive or non-convulsive status epilepticus)	Immediate anticonvulsant therapy
Infection (meningitis, encephalitis)	Lumbar puncture and empiric antimicrobial therapy
Endocrinopathies	• Adrenal crisis. Intravenous hydrocortisone (100 mg IV bolus, followed by 200 mg over 24 h), along with rapid intravenous isotonic saline resuscitation, and correction of hypoglycemia if present • Myxedema coma. Intravenous levothyroxine (loading dose of 200–400 mcg), empiric intravenous glucocorticoids, and comprehensive supportive care

Table 2 Full Outline of UnResponsiveness (FOUR) score and Glasgow Coma Scale (GCS)

	Glasgow Coma Scale (GCS)	Full Outline of UnResponsiveness (FOUR) Score
Domains Assessed	Eye opening, verbal response, motor response	Eye response, motor response, brainstem reflexes, respiratory pattern
Scoring range	3–15 (3 subscales)	0–16 (four 0–4 subscales)
Guidelines	None	Operational
Brainstem function evaluation	Indirect	Direct assessment of pupillary, corneal, and cough reflexes
Subtle signs of awareness	Limited	Direct assessment of visual pursuit—diagnosis of LIS and MCS
Respiratory assessment	Not assessed	Assesses spontaneous respiratory patterns
Usefulness in intubated patients	Limited	Fully applicable
Predictive value	Validated; less sensitive to subtle brainstem decline	Often superior for ICU prognostication

comprehensive workup guided by the neurologic exam allows for early diagnosis and targeted therapy.

History and initial evaluation

Initial coma assessment prioritizes airway, breathing, and circulation [28]. First, if the airway is unprotected, assess and secure the airway, if indicated. Second, for intubated patients, confirm end-tidal CO_2 and ensure normocapnia (i.e., $PaCO_2$ 35–45 mmHg). Third, correct cardiovascular instability, administering a fluid challenge with isotonic solutions if indicated. Fourth, rule out and correct hypoglycemia, if indicated. Starting from the prehospital and emergency department phases, a focused history should be collected from family, witnesses, or medical records to identify potentially reversible causes, such as intoxications, metabolic issues, or infections. A quick yet thorough neurological and systemic examination should specifically look for trauma, drug use, fever, or signs of respiratory, hepatic, and/or renal failure, as these may guide diagnosis.

Neurological examination and clinical scoring

The examination of patients with coma must include a systematic assessment of the level of consciousness, brainstem reflexes, motor responses, and respiratory patterns (Fig. 3). The Glasgow Coma Scale (GCS) remains widely used [12]; however, its limitation in the evaluation of verbal responses in intubated patients and brainstem function has led to the adoption of the Full Outline of UnResponsiveness—FOUR—score, which incorporates eye tracking, breathing patterns, and brainstem reflexes [30]. The FOUR score has excellent inter-observer consistency and has better predictive value than the GCS in patients with very low GCS score [32] (Table 2). When

combined, clinical signs (especially pupil size and reactivity, gaze deviation, and posture) can be more effective than isolated signs in indicating a focal cerebral cause of coma (Fig. 3). To enable early and accurate differentiation between coma and related disorders of consciousness (VS/UWS, MCS) in the ICU setting, faster, adapted versions of the Coma Recovery Scale—Revised (CRS-R) have recently been developed, including the CRS-R for Accelerated Standardized Testing (CRSR-FAST) [33] and the simplified Evaluation of CONsciousness Disorders (SECONDs) [34]. Repeated assessments are crucial for systematically disentangling these clinical conditions, as fluctuations in arousal and responsiveness may lead to misdiagnosis when diagnosis is based on a single evaluation [35].

Harnessing Electrophysiology

Electroencephalography (EEG) is a core component of the diagnostic and prognostic assessment of patients with coma across all related etiologies [36]. Although formal guidelines for EEG use and interpretation pertain mostly to anoxic coma [37], the EEG is part of the clinical evaluation of coma of any cause.

Electrographic seizures

The primary indication for recording EEG in patients with coma is the detection of electrographic seizures and nonconvulsive status epilepticus (NCSE). Indeed, the vast majority of seizures detected in the ICU are subclinical, emphasizing the importance of continuous EEG (cEEG) for timely diagnosis and management. Hence, cEEG detects up to 18% for nonconvulsive seizures in mixed coma populations [36]. Although early EEG features obtained during the first hour of recording can already provide meaningful seizure-risk stratification, seizure detection can require prolonged EEG monitoring for hours or even > 24 h in a subset of patients in the ICU [36]. In this context, the 2HELPS2B score, derived from an initial screening EEG, can guide monitoring duration: patients with a score of 0 have a seizure risk < 5% and may be adequately screened with a short recording (~ 1 h), whereas those with a score of 1 may benefit from ~ 12 h monitoring, and patients with a score ≥ 2 generally warrant prolonged/continuous EEG (≥ 24 h) due to higher seizure risk [38, 39]. The implementation of such quantitative approaches to evaluate the risk–benefit of prolonged EEG monitoring for seizure detection promises to improve decision-making and optimize the use of existing clinical resources.

Higher seizure burden (quantified as cumulative duration or peak epileptiform activity) is associated with worse neurological outcomes, and despite the lack of evidence from randomized trials [37, 40], the American Clinical Neurophysiology Society and the European Society of Intensive Care Medicine suggest considering cEEG for patients with coma to optimize management of seizure burden [41, 42]. However, whether aggressive reduction of seizure burden through specific antiepileptic treatment protocols guided by cEEG improves short- or long-term neurological outcomes in critically ill patients remains unknown [42, 43].

Discrete EEG signatures

Some more specific EEG patterns can inform about the etiology of coma and can guide therapeutic interventions or prioritize the further assessment through other imaging modalities (Fig. 2). Generalized periodic discharges with triphasic waves refer to periodic, bilaterally synchronous EEG patterns that are not inherently ictal but may often indicate toxic/metabolic encephalopathy [44]. Lateralized periodic discharges (LPDs) suggest an acute focal cortical lesion [45] and commonly arise at the interface between damaged cortex and adjacent, relatively preserved tissue, often corresponding to the ischemic penumbra or perilesional zone, and are thought to reflect excitotoxicity and ongoing risk for secondary injury, including NCES. Furthermore, bilateral periodic discharges point to bilateral or diffuse structural disease, and posterior-dominant alpha coma and some beta-coma patterns may indicate brainstem lesions.

Bedside EEG assessment of thalamocortical disconnection

The use of bedside EEG to assess thalamocortical network integrity arises from its capacity to noninvasively capture large-scale cortical oscillations that are shaped by ascending thalamic projections and corticothalamic loops. Because functional connectivity between the thalamus and cortex is central to the maintenance of arousal and awareness (see "Pathophysiological underpinnings"), bedside EEG recording provides rapid and repeatable indices of coma severity. Hence, across etiologies, delta activity predominates and becomes slower and more continuous as coma deepens. With further deterioration, the background grows discontinuous and evolves into burst-suppression; longer inter-burst intervals reflect greater severity [46]. The EEG may indicate further degeneration till an electrocerebral inactivity or isoelectric silence [36]. A suppressed or burst-suppressed background with or without periodic discharges in the absence of potential confounders is considered as a predictor of poor outcome [47].While these patterns have been mostly reported through the visual inspection of raw EEG, characterizing resting-state EEG dynamics with power spectral analysis, including the ABCD empirical model (Fig. 4), can provide relevant information for

patient stratification according to their inferred thalamocortical network integrity (Fig. 1):

- **A.** *No peaks above delta (< 4 Hz)*; indicates complete thalamocortical disruption; observed in patients with coma with limited benefit of therapeutic escalation or VS/UWS.
- **B**. *Theta (4–8 Hz) peak present*; reflects severe thalamocortical disruption; can be identified in coma, VS/UWS or MCS patients.
- **C**. *Both theta and beta (13–24 Hz) peaks*; suggest moderate thalamocortical disruption; mostly associated with coma recovery and MCS.
- **D**. *Alpha (8–13 Hz) and beta peaks*; consistent with normal thalamocortical function; generally, indicates consciousness recovery. To be distinguished from "alpha coma", a rare but well-defined non-reactive anterior EEG pattern, mostly reported in anoxic coma patients with unfavorable outcome [48].

The ABCD EEG classification is supported by recent evidence suggesting that longitudinal improvements in ABCD grade parallel neurological recovery, in the specific context of several structural brain injuries (e.g., traumatic, anoxo-ischemic, and subarachnoid hemorrhage) [49–51]. Hence, as suggested by the B-ICONIC (Biomarkers of ICU Neurological Injury and Consciousness) multicenter research program [52], the ABCD model provides a conceptual and empirical bridge between EEG spectral features and the functional status of thalamocortical networks, offering a valuable tool for probing the depth of functional disconnection at the bedside of severely brain-injured patients. From a data-driven standpoint, recent machine learning and deep learning resting-state EEG studies achieve promising diagnostic and prognostic performance [53] (see below).

Neuroimaging insights

Clinical examination remains the cornerstone for determining the most appropriate neuroimaging modality in patients with coma. Bedside neurological findings not only inform diagnostic hypotheses but also guide the selection between computed tomography (CT) and magnetic resonance imaging (MRI), depending on the suspected underlying pathology (Fig. 5). In the presence of focal neurological deficits, structural brain lesions must be urgently excluded. In such contexts, the American College of Radiology and the Emergency Neurological Life Support [54] emphasize the use of noncontrast CT as the first-line imaging modality due to its rapid acquisition, broad availability, safety and high sensitivity for acute hemorrhage, mass effect, hydrocephalus or large territorial infarction. MRI may subsequently be indicated to further characterize lesions when CT findings are inconclusive. When brainstem clinical abnormalities are observed, imaging strategies should prioritize detailed evaluation of posterior fossa structures, and MRI with diffusion-weighted imaging (DWI) is generally preferred when feasible and clinically stable. Conversely, when the clinical presentation suggests a non-structural or diffuse brain injury—such as toxic-metabolic encephalopathy, anoxic injury, or systemic causes—initial CT imaging may be performed to exclude unexpected structural lesions. Nevertheless, MRI may provide superior detection of diffuse hypoxic-ischemic injury, subtle cortical or deep gray matter abnormalities, or microstructural changes not visible on CT.

It is important to consider whether a contrast CT is required in addition to noncontrast (especially if the plain CT does not explain the cause of coma), and, if so, the timing of this contrast to avoid missing important diagnoses which have time-critical treatment options. Indeed, CT angiogram and CT perfusion may identify whether an ischemic stroke has occurred and whether it is amenable to thrombolysis or thrombectomy [55]. In particular, CT angiogram is urgently required in patients who have a neurological examination and clinical picture consistent with a basilar artery thrombus as CT perfusion is often difficult to interpret in the brainstem and/or the field of view may not have adequate coverage [42]. CT venograms are required to assess for venous sinus thrombosis where filling defects in the sinuses may be observed [56]. Contrast may also reveal aneurysms, arteriovenous malformations, tumors and abscesses.

Conventional structural MRI sequences, by which lesions can be visualized, enable important insights into the degree of structural damage and help predict outcome [57]. MRI sequences such as DWI are highly sensitive in identifying early ischemic changes that may not be visible on CT as well as vasogenic edema characteristic of posterior reversible encephalopathy syndrome (PRES) [58]. Fluid-attenuated inversion recovery (FLAIR) sequences help identify inflammatory lesions and brain edema. More advanced sequences including diffusion MRI variants (dMRI), largely diffusion tensor imaging (DTI), help investigate the structural integrity of the brain by characterizing the movement of water molecules in tissue environments which changes after injury, and can enable key insights into pathophysiology, help predict neurologic recovery [59] and aid neuroprognostication [22, 23] (Fig. 1).

It is important to recognize the limited availability of advanced neuroimaging techniques in resource-constrained setting worldwide. The B-ICONIC guidelines specifically address these challenges [52],

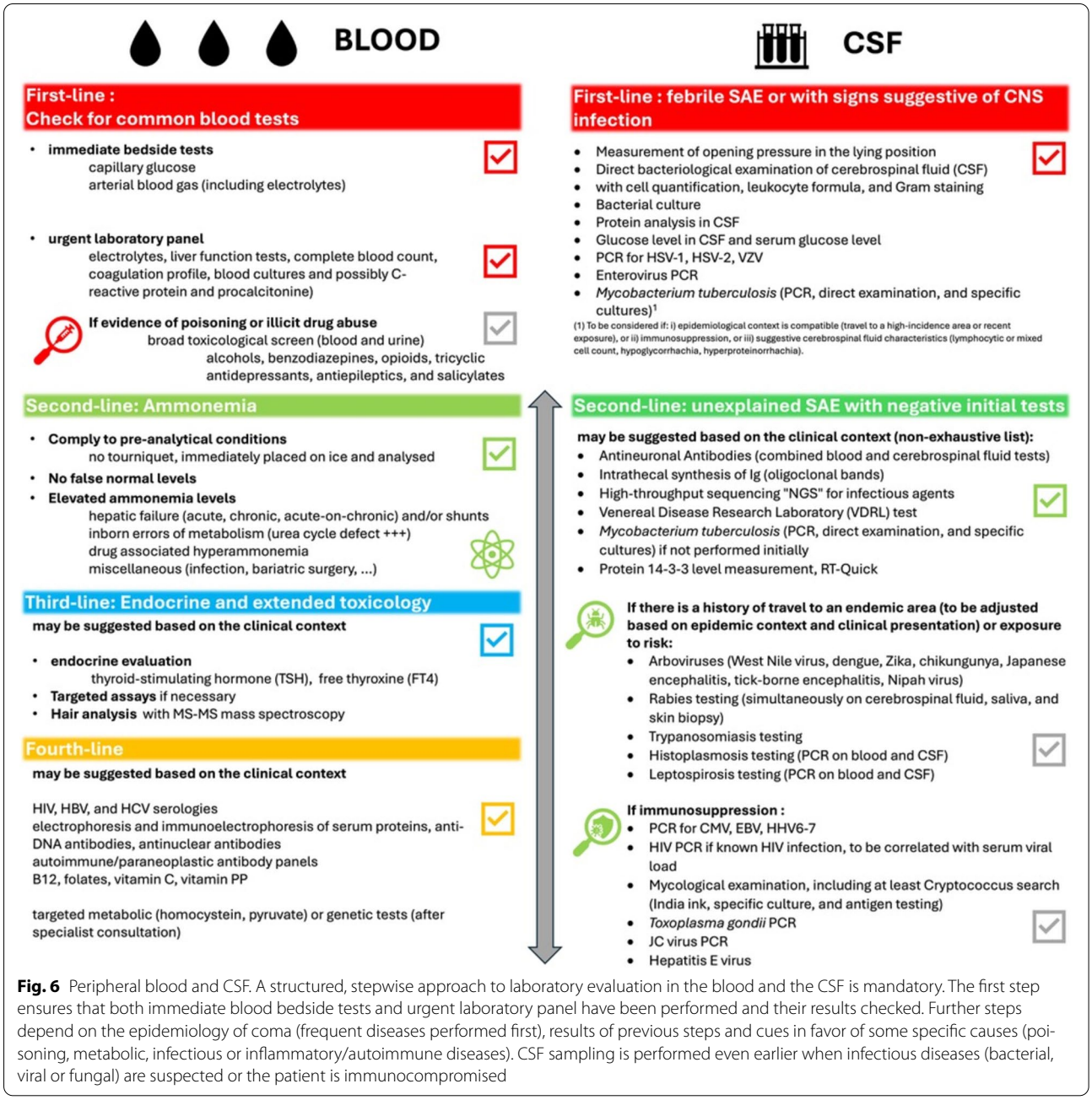

Fig. 6 Peripheral blood and CSF. A structured, stepwise approach to laboratory evaluation in the blood and the CSF is mandatory. The first step ensures that both immediate blood bedside tests and urgent laboratory panel have been performed and their results checked. Further steps depend on the epidemiology of coma (frequent diseases performed first), results of previous steps and cues in favor of some specific causes (poisoning, metabolic, infectious or inflammatory/autoimmune diseases). CSF sampling is performed even earlier when infectious diseases (bacterial, viral or fungal) are suspected or the patient is immunocompromised

offering practical, evidence-informed guidance that remains applicable even in settings without specialized personnel or advanced diagnostic resources.

CT vs MRI: when to choose which modality

- Clinical examination, patient stability and camera availability are critical in selecting the optimal neuroimaging modality.
- Noncontrast CT is advised emergently in coma patients with presumed structural causes after initial stabilization [60]. This modality is fast, broadly available and highly sensitive for brain hemorrhage, mass effect, hydrocephalus and fractures. Normal CT does not exclude many severe etiologies (early ischemic stroke, PRES, venous thrombosis, encephalitis, diffuse axonal injury).
- MRI is best suited for subacute evaluation of an undetermined cause due to availability constraints and longer acquisition times, but provides superior

sensitivity to CT for ischemia, small structural anomalies, and posterior fossa lesions [61].

- In patients with known intracranial pathology, both CT and MRI can be appropriate, with MRI preferred when feasible [60].
- When non-structural causes are suspected (toxic, metabolic), imaging may be discretionary. MRI can identify subtle structural changes when indicated.

Laboratory findings

A structured, stepwise approach to laboratory evaluation in a coma of unknown origin is essential [2]. The challenge lies in balancing the time required to obtain results with the need for immediate therapeutic decisions. It is mandatory as a first step to ensure that both immediate bedside tests—capillary glucose and arterial blood gas (including electrolytes)—and the urgent laboratory panel (creatinine and blood urea nitrogen (BUN), liver function tests, complete blood count, coagulation profile, blood cultures and possibly C-reactive protein and procalcitonin) have been performed and their results checked (Fig. 6).

In the absence of any clear diagnostic direction, plasma ammonia should be measured in a second step with results ideally available within 1 h. Hyperammonemia may indicate hepatic failure—acute liver failure, chronic liver disease, acute-on-chronic decompensation—, or rare inborn errors of metabolism, particularly urea cycle disorders such as ornithine transcarbamylase deficiency that need urgent therapeutic intervention [27, 62]. Other causes are also possible. It should be noted that falsely elevated levels are possible (if suspected, resample), but not falsely normal values. If hyperammonemia is associated with elevated lactate without any obvious cause of hypoxia, a mitochondrial disorder should be suspected.

On the basis of the patient's medical history and clinical assessment, or in the absence of meaningful diagnostic indicators, endocrine evaluation—thyroid-stimulating hormone (TSH) and free thyroxine (FT4), and cortisol levels if an Addisonian (adrenal) crisis is suspected. Although endocrine coma is often accompanied by clinical signs or electrolyte disturbances, toxic encephalopathies may occur without a history of drug ingestion or substance abuse. In such cases, a broad toxicological screen (blood and urine) is warranted, covering common agents such as alcohols, benzodiazepines, opioids (buprenorphine, methadone), tricyclic antidepressants, antiepileptics (pregabalin), MDMA, ketamine, cocaine, gamma-hydroxybutyrate, (meth-)amphetamines and salicylates. Targeted assays should be added if necessary. Hair analysis using tandem mass spectroscopy (MS/MS) may identify previous unsuspected exposures that are not detected by earlier blood testing. However, the diagnostic yield of such advanced techniques is limited by their high cost and the fact that results typically require up to 2 weeks to be obtained.

Further investigations should ideally be guided by cerebrospinal fluid (CSF) analysis, which can be conducted in parallel. In the presence of CSF pleocytosis (CSF white cell count > 5/mm^3), HIV, HBV, and HCV serologies as well as autoimmune/paraneoplastic antibody panels should be considered. Without pleocytosis, a metabolic or toxic cause is more likely, and targeted metabolic or genetic tests may be proposed after specialist consultation [42].

Lumbar puncture and CSF

Timely lumbar puncture (LP), performed when safe and integrated into a multimodal diagnostic pathway, can yield diagnostic information and directly guide therapy. LP remains a cornerstone in the evaluation of coma of unknown origin, particularly when suspicion of CNS infection or inflammatory disease is high (e.g., subacute or acute onset of headache, fever, altered mental status, with or without associated signs). The decision to perform CSF analysis should be guided by clinical presentation and biological and neuroimaging findings. Neuroimaging to exclude contraindications to LP is recommended only for patients with severely depressed consciousness and suspected herniation, focal neurologic deficits, new-onset seizures, or immunocompromised status [63]. Several CSF parameters—including opening pressure; cell count with differential (polymorphonuclear cells vs lymphocytes); glucose with simultaneous serum glucose measurement; protein; and lactate—help distinguish bacterial from viral infections and may suggest non-infectious conditions. Gram stain and bacterial cultures should be performed systematically, with India ink examination added in immunocompromised patients. Bacterial meningitis typically presents with pleocytosis with a predominance of polynuclear cells, elevated protein, and reduced glucose concentration, although subtler abnormalities may be observed. Viral encephalitis typically demonstrates lymphocytic pleocytosis, moderate protein elevation, and normal glucose levels. Of note, absence of CSF pleocytosis does not exclude the diagnosis of viral encephalitis [64], particularly in immunocompromised hosts. Polymerase chain reaction (PCR) testing has revolutionized the detection of viral and bacterial pathogens, enabling rapid and sensitive identification of herpesviruses, enteroviruses, and *Mycobacterium tuberculosis*. The BioFire® FilmArray Meningitis/Encephalitis panel simultaneously detects 14 common bacterial, viral, and fungal pathogens in about 1 h [65]. Clinical studies suggest that mPCR reduces the time to

targeted therapy, decreases unnecessary antimicrobial exposure, and facilitates early differentiation between infectious and non-infectious coma [66]. Nonetheless, limitations include a restricted pathogen spectrum, variability in sensitivity across organisms, and occasional false positives, particularly for herpesviruses with latent or unclear clinical significance (e.g., HHV-6), and false negatives, notable for HSV-1. Accordingly, mPCR results must always be interpreted in conjunction with clinical features, conventional microbiology, and neuroimaging. Beyond infectious causes, CSF analysis provides critical insights into autoimmune and paraneoplastic encephalitis. These conditions may manifest with mild lymphocytic pleocytosis, mildly elevated protein levels, intrathecal IgG synthesis, and/or oligoclonal bands. The detection of neuronal antibodies in CSF has become essential for diagnosis and therapeutic guidance. Consensus criteria emphasize that both serum and CSF should be tested, as certain antibodies—particularly anti-NMDAR—are more sensitive and specific in CSF [67]. Autoantibody testing should be performed in paired serum and cerebrospinal fluid using validated cell-based assays targeting neuronal surface antibodies, with complementary tissue-based or onconeural antibody testing when appropriate. Testing should ideally precede immunotherapy but should not delay treatment in highly suggestive cases. Results must be interpreted in light of the clinical phenotype and ancillary investigations, and repeat testing should be considered when suspicion remains high despite negative initial results [68]. CSF analysis also plays a role in suspected malignant infiltration, where cytology and flow cytometry may confirm leptomeningeal disease, although repeated sampling may be necessary to improve sensitivity.

Practical insights into CSF analysis

- Lumbar puncture with CSF analysis is a cornerstone of the diagnostic workup for coma of unknown origin when a central nervous system infection or inflammatory disorder is suspected. Contraindications to lumbar puncture should always be assessed before the procedure.
- The absence of CSF pleocytosis does not exclude viral or autoimmune encephalitis.
- Results of multiplex CSF PCR panels must be interpreted in light of the clinical context, as both false-positive and false-negative results may occur.
- When autoimmune encephalitis is suspected, paired serum and CSF antibody testing should be performed.
- Repeat lumbar puncture should be considered when initial CSF findings are nondiagnostic and clinical suspicion remains high.

Future and perspectives

Substantial progress has been achieved in recent years in understanding the abolition and recovery of consciousness following severe brain injury. Most of the available evidence derives from studies of prolonged disorders of consciousness (VS/UWS, MCS) [11]; however, more recent research focusing specifically on the coma state has raised hope for more accurate diagnosis and improved clinical management. Accordingly, these emerging technologies offer novel opportunities to detect and monitor covert and overt recovery of consciousness from coma [69], to quantify frontoparietal and thalamocortical integrity in real time [19–21, 70], and to identify personalized therapeutic interventions that specifically target the restoration of higher order cognitive abilities, including non-behavioral communication [71]. Nonetheless, most of these methods still require multicenter prospective validation before integration into standard clinical care.

Data multidimensionality: from burden to benefit

Heterogeneity is recognized as a major barrier in efforts to improve the care and outcomes of patients with coma [2, 3]. This heterogeneity arises because coma can result from diverse etiologies and can affect different components of frontoparietal and thalamocortical networks, leading to a wide spectrum of clinical severity and prognosis. Critically, the data required to characterize and analyze these clinical presentations are complex and high dimensional, yet have historically been reduced to clinical variables alone. This simplification has hindered precision medicine approaches in the field and favored misleading "one-size-fit-all" management strategies. Notably, recent advances in machine learning and AI offer the potential to leverage the full breadth of available multimodal data during the acute phase of coma. These include continuous EEG, different evoked potential paradigms, automated pupillometry, functional Near InfraRed Spectroscopy (NIRS), blood-based biomarkers, and portable MRI which brings structural and diffusion imaging into ICUs, enabling serial assessments in unstable patients [72]. In addition, an emerging domain of assessment is the decoding of behavioral features at high temporal resolution. Continuous 2D accelerometry/actigraphy, wearables, and video-based analytics of face, pose, and movement—can yield quantitative assessments of arousal and prognosis. These dense time series reveal clinically latent current and future states and

therapeutic responses, providing actionable windows for intervention [73].

However, determining the clinical impact of these approaches requires (1) standardized data structures to enable sharing/reproducibility; (2) prospective, protocolized validation; and (3) integration into bedside workflow with human-in-the-loop oversight. Frameworks like Brain Imaging Data Structure (BIDS) can accommodate multimodal curation; evaluation should follow SPIRIT-AI and CONSORT-AI extensions with decision-focused endpoints (diagnostic accuracy, time-to-treatment, prognostic calibration, net benefit) [74, 75].

Neuroimaging beyond structural evaluation

As a promising lead, both stimulus-based functional MRI (fMRI) and EEG may detect cognitive motor dissociation (CMD)—patients clinically diagnosed as unresponsive but demonstrating the capacity to willfully modulate activity within specific brain regions in response to commands thought these neurotechnologies. CMD [69, 76] and resting-state brain activity [20, 70] are associated with outcome and emergence from coma. However, it should be noted that factors including patient movement in the scanner [77], sedation [54], and toxic-metabolic derangements [78] may artificially reduce connectivity and probably of CMD detection. Therefore, while preserved connectivity and/or CMD indicates an intact substrate for clinical improvement, the presence of diminished functional connectivity or lack of CMD needs cautious interpretation [54]. Further validation and improvements in acquisition and analysis are required before such imaging could be used widely in clinical practice.

Moving from phenotypes to endotypes

Many lines of research demonstrate that discrete syndromic labels for coma do not map to biological reality. Paradigms such as state-space modeling, which considers a matrix of dynamically evolving neural states, might provide a more accurate representation of brain dysfunction. Multimodal assessment—integrating neurophysiology, neuroimaging, biochemical profiling, genomics/other omics, and trajectory modeling—can map patients to mechanistically coherent states that more accurately capture biological complexity and guide testing and treatment [79–81]. Digital twins powered by transformer-based foundation models can be trained with clinical notes, waveforms, imaging, and omics data to infer latent states, simulate counterfactual interventions, and forecast recovery trajectories. These models achieve cross-site generalization with minimal task-specific training, enabling deployment across heterogeneous healthcare [82, 83].

Collectively, these advances can transform coma management from syndromic classification (i.e., phenotypes) to mechanistic understanding (i.e., endotypes), from episodic assessment to continuous monitoring, and from population-based protocols to individualized precision medicine.

Conclusion

Coma of unknown origin requires a structured, time-critical, and physiologically informed diagnostic strategy. Early stabilization must be followed by a systematic clinical examination capable of localizing dysfunction and guiding the appropriate sequence of investigations. Neuroimaging, EEG, laboratory testing, and CSF analysis each provide complementary insights and should be deployed rationally rather than indiscriminately. Identifying reversible causes at the earliest possible stage is essential to prevent secondary brain injury and optimize neurological outcomes.

The pathophysiology of coma extends beyond focal lesions to include network-level disruptions of thalamocortical and frontoparietal systems. This mechanistic understanding supports a multimodal approach integrating electrophysiology, advanced imaging, and targeted laboratory investigations. Emerging technologies—including continuous physiological monitoring, network-level biomarkers, portable MRI, and artificial intelligence—offer the potential to map brain-state transitions in real time and move coma care toward individualized, precision-based management.

A rigorous, reassessment-driven diagnostic pathway, grounded in neurobiology and adapted to the ICU environment, is therefore critical for improving the diagnosis, treatment, and prognostication of patients presenting with coma of unknown origin.

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According to the CRediT taxonomy, the specific contributions are as follows: Stein Silva: conceptualization, writing—original draft, writing—review and editing, supervision, project administration; Miriam Teggiari: writing—original draft; Giuseppe Citerio: conceptualization, writing—original draft, writing—review and editing; Robert David Stevens: writing—original draft;

Marzia De Lucia: writing—original draft, writing—review and editing; Virginia Newcombe: writing—original draft; Aurore Thibaut: writing—original draft, writing—review and editing; Nicolas Weiss: writing—original draft; review and editing; Romain Sonneville: conceptualization, writing—original draft, writing—review and editing, supervision, project administration. All the authors have read and approved the final manuscript.

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