Metabolic Encephalopathies and Delirium

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CLINCIAL CASE

A 57 year-old female with chronic low-back pain from a previous car accident was admitted to the Medical ICU after been found unresponsive at home with 20 pills of methadone missing from her drug box. She was severely hypoxic when EMS arrived with first recorded O2 saturation of < 50% and in the Emergency Department she was found to be in acute liver and renal failure with rhabdomyolysis (transaminases in 4-6,000 IU/L range, ammonia 101 µmol/L, creatinine 5.9 mg/dL and creatine phosphokinase initially 5,000 IU/L). She was coagulopathic with INR 2.37 and with cerebral edema on head CT, but with open basilar cisterns. Pt was intubated since she was comatose. Neuro-exam consisted of extensor posturing to pain (GCS 4T), but intact brainstem reflexes. She was transferred to the Neuro-ICU, where a fiberoptic intracranial pressure monitor, an arterial line and a dialysis catheter were placed simultaneously after reversal of the coagulopathy with Factor VII and Prothrombin Complex Concentrate. She underwent sustained low-efficiency dialysis (SLED) with high sodium bath (150 mEq/L) and was administered rifaximin and lactulose per nasogastric tube. EEG initially showed severe encephalopathy with triphasic waves. Within the next few days, ammonia and liver enzymes decreased, renal function improved, the ICP monitor was removed and clinically she opened the eyes and eventually followed commands. She was eventually extubated and discharged from the Neuro-ICU 5 days post-admission.

OVERVIEW

The term encephalopathy derives from the Greek encephalos (brain) and pathos (suffering or experience). In current times, acute encephalopathy is synonymous with acute confusional state, acute organic brain syndrome or delirium. Kinnier Wilson was the first to coin the term metabolic encephalopathy to describe the clinical presentation of a global cerebral dysfunction induced by systemic factors. This is a common encounter in hospitals and especially Intensive Care Units, where it can begin as a subtle cognitive change usually missed initially, progress to a readily detectable delirium and eventually resolve or lead to coma and death.

The incidence of delirium has been estimated between 5-40% for hospitalized patients in general and between 11-80% for critically ill patients. Other studies have reported a lower incidence of about 30%, after the exclusion of patients maintained in purposeful drug-induced sedation.

Many etiologies of acute encephalopathy can be easily detected with neuroimaging as a well visualized structural lesion (ischemic stroke, intracerebral or subarachnoid hemorrhage, tumor etc). A frequent reason for a Neurological consultation, however, remains the non-structural, metabolic syndrome and its management considerations. This will be the focus of this chapter.

ETIOLOGY AND RISK FACTORS

The various etiologies of metabolic encephalopathy are presented in Table 1. In general, there could be divided into drug intoxication or withdrawal (frequently from illegal drugs), electrolyte and glucose abnormalities, major organ dysfunction (such as liver, kidneys, lungs, endocrine), nutritional deficiencies, exposure to extraneous toxins, paraneoplastic syndromes and sleep or sensory deprivation.

Risk factors that have been associated with delirium in hospitalized, critically ill patients include [1]:

- Older age (more than 70 years),
- Male gender,
- Poor functional status,
- Malnutrition,
- Substance abuse
- Pre-morbid medical conditions or cognitive impairment
- Polypharmacy, including medications that affect neurotransmitters (such as anticholinergic or dopaminergic)
- Physical restraints
- Visual or hearing impairment
- Prior history of delirium

DIAGNOSIS

Despite the protean symptomatology of delirium, specific diagnostic criteria have been developed, which are presented in Table 2. The diagnosis can be missed in mild forms, but any presentation which includes alteration in the level of consciousness (agitation or sedation), attention impairment (distractability, perseveration), fluctuation of the symptoms in time and severity (with worsening during the night or reversal of sleep-wake), presence of hallucinations, disorientation or perceptual distortions, as well as disorganized thought process (occasionally incoherent speech or non-pre-existing memory disturbances) should alert the physician of its presence.

Standardized delirium detection scales have also been used, but are not specific for the etiology of the metabolic encephalopathy. These include the Confusion Assessment Method for the Intensive Care Unit (**CAM-ICU**) [2] and the Intensive Care Delirium Screening Checklist (**ICDSC**) [3]. Using these scales one can detect delirium, but cannot necessarily differentiate between hepatic or septic or uremic encephalopathy, for example, because all could present with similar signs and symptoms.

Therefore, a detailed history especially through relatives, by-standers or co-workers can be of immense help, as well as review of previous hospital admission or clinic data. The clinical exam would also reveal focality in the neurological part when structural brain lesions are present, but in the vast majority of cases non-focal exam with alteration of vital signs (tachycardia, hypotension, hypertension, tachypnea) in case of a metabolic encephalopathy. A detailed systematic exam may also reveal clues for the etiology of the encephalopathy. For example, fever and nuchal rigidity for meningitis, clammy pale extremities with hypotension in shock, jauntice in hepatic encephalopathy, fruity breath odor from acetone expiration in diabetic ketoacidosis, blue gum with lead, Mees'lines with arsenic and acrodynia with mercury intoxications [4]. One should not forget, however, that even metabolic derangements can suggest focality, such as focal-onset seizure with hypoglycemia or asymmetric ophthalmoplegia and ataxia with thiamine deficiency.

A basic or extended laboratory workup may then reveal the cause (Table 3). One should remember that many drug levels can be measured only in specialized laboratories, therefore extra serum should be stored in case the culprit is not revealed after the routine, first-pass evaluation. Electroencephalography (EEG) may show triphasic waves which usually occur with hepatic or uremic encephalopathy, but are not specific. Neuroimaging studies can also help to exclude structural lesions and also allow a safer lumbar puncture, as well as occasionally narrow the potential etiologies of toxometabolic encephalopathies. MRI of the brain may reveal specific findings in conditions such as central pontine myelinolysis from rapid hyponatremia correction, carbon monoxide poisoning, methanol, ethylene glucol, cyclosporine or metronidazole toxicity. MR spectroscopy can be used to detect the decreased choline and myoinositol and the increased glutamine and glutamate in hepatic encephalopathy, but the clinical application of these findings are questionable [5].

GENERAL TREATMENT FOR ACUTE METABOLIC ENCEPHALOPATHIES

Treating delirium is considered a medical emergency. Assessment of airway, breathing and circulation is always the first step, followed by a detailed neurological examination in parallel with laboratory and neuroimaging studies. The identification of the underlying cause is of utmost importance. Preventing measures in order to avoid escalation of symptoms, such as patient reorientation, noise reduction, avoidance of unnecessary procedures, decrease of restraint use, promotion of sleep or exposure to daylight and limiting sensory deprivation (glasses, hearing aids) are also helpful. Pain

control is important, since inadequate analgesia is associated with delirium. Antiphychotics, such as haloperidol in low, frequent doses (1-5 mg IV q4-6 hours) with monitoring of the electrocardiographic QTc interval and normal magnesium levels, quetiapine (25-100 mg/day po) or olanzapine (2.5-7.5 mg/day po) are frequently used, although not approved by the FDA for this indication and with recent data suggesting increased mortality with their use in the elderly [6]. Extrapyramidal movement disorders and neuroleptic malignant syndrome are also potentially serious side-effects of these drugs. Benzodiazepines should be used in alcohol or cocaine withdrawal cases. Randomized trials comparing dexmedetomidine to either midazolam or lorazepam showed either no difference or lower prevalence of delirium in the dexmedetomidine arm, as well as fewer days with delirium [7]

SELECTED METABOLIC ENCEPHALOPATHIES

Sepsis-associated encephalopathy (SAE)

Sepsis is often associated with delirium. SAE has been reported in 9-71% of patients with sepsis and may lead to increased mortality and morbidity. The pathophysiology is very complex. Activation of the vagus nerve by visceral inflammation leads to brainstem and hypothalamic activation (nucleus tractus solitaries, paraventricular nuclei). Circumventricular organs, lacking blood brain barrier (BBB), are also activated by systemic inflammation. Both signal behavioral, neuroendocrine or neurovegetative alterations, which may modulate neurosecretion and neurotransmission, constituting the substratum of SAE [8]. By the same token, lipopolysaccharides and proinflammatory cytokines activate the brain vessel endothelium, which leads to altered vascular microcirculation and breakdown of the BBB with passage of neurotoxic factors to the brain parenchyma, affecting autoregulation of cerebral blood flow, inducing macro-ischemias/hemorrhages and at a cellular level enhancing oxidative stress and promoting mitochondrial dysfunction and apoptosis [8,9].

SAE clinically is similar to any other encephalopathy, with agitation, asterixis, tremor, paratonic rigidity, multifocal myoclonus and even coma. Special attention should be paid to the presence of neck rigidity and focality in the exam, which should trigger early neuroimaging and lumbar puncture (if no focal lesion is detected, basilar cisterns are open and non-communicating hydrocephalus is excluded). EEG will help eliminate non-convulsive seizures which can occur during sepsis or enhanced by antibiotics used in the treatment of the infection (imipenem, cefepime, metronidazole etc, especially in the context of renal failure with higher serum concentrations [10,11]).
No specific treatments for SAE other than treating the systemic illness exist [12]. However, patients with GCS < 13 treated with human recombinant activated Protein C have shown lower blood S100b concentrations (a glial marker of brain damage) than those who did not receive it [13].

Hepatic encephalopathy (HE)

HE has been associated with acute or progressive or chronic liver failure. Cerebral edema, the most fearsome neurologic complication, is both of the cytotoxic and vasogenic types. The former is related to astrocytic swelling because of neurotoxin accumulation (ammonia, short-medium chain fatty acids, phenols, mercaptans), false neurotransmitters and activation of GABA receptors by endogenous benzodiazepines (endozepines). The latter is related to alterations in the blood-brain-barrier permeability, increased cerebral blood flow and systemic inflammation. A grading system has been developed using clinical criteria (Table 4), but one needs to be aware that the transition from grade 1 to 4 may be more gradual with chronic liver failure than with acute [14]. Diagnosis is supported by elevated ammonia, neuroimaging showing diffuse edema of the brain and hyperintensive signal in the globus pallidus, subthalamic area and midbrain in T1-weighed MRI sequence and triphasic waves in the EEG. Therapeutic measures include ammonia lowering regimens (lactulose and non-absorbable antibiotics [neomycin, rifaximin [15] or metronidazole], intracranial pressure monitoring and management with placement of ICP monitors after correction of the coagulopathy (factor VII, prothrombin complex concentrate), sedation with low-dose propofol, mannitol and hypertonic saline (with serum osmolality goals of < 320 mosm/L or osmolar gap < 20), flumazenil to counteract any endozepine action [16], hyperventilation (if patient is too sedated to develop the expected respiratory alkalosis), normo- or mild hypothermia, slow renal replacement therapy if hepatorenal syndrome occurs (usually continuous venovenous hemofiltration or sustained low-efficiency dialysis to avoid rapid osmotic shifts) and lastly, orthotopic liver transplantation.

Uremic encephalopathy (UE)

UE is usually more severe after acute renal failure, but can also be witnessed with chronic renal failure. Because acute renal failure often complicates sepsis, it may difficult sometimes to differentiate UE from septic encephalopathy. Accumulation of dialyzable uremic toxins (urea, guanidine compounds, hippuric acid, polyamines, phenols, indolic acids, myoinositol) have been implicated in the pathogenesis, in addition to sodium-potassium-ATPase dysfunction and increased parathyroid hormone with elevation of intracellular sodium and calcium, respectively. The guanidine compounds have been shown to exert antagonism in the GABAergic receptors and have an agonistic effect in the NMDA receptors, leading to enhanced cortical excitability, which may be the opposite to HE. A distinct dialysis disequilibrium syndrome may also occur in patients with high pre-dialysis urea and metabolic acidosis who undergo rapid hemodialysis with fast osmolar shifts and development of brain edema. This may be due to development of an osmolar gradient favoring water influx to the brain after rapid peripheral urea decrease or to an increased production of idiogenic intracellular osmoles.

Clinically, the syndrome starts with subtle mental and emotional changes and can progress to full blown delirium, seizures and coma. Motor phenomena, such as action tremor, asterixis, hypereflexia, myoclonus, as well as anorexia and, in longstanding cases, peripheral neuropathy can also be part of the clinical evolution. Neuroimaging may reveal diffuse cerebral atrophy and the EEG generalized slowing with triphasic waves, paroxysmal frontally-predominant high voltage delta waves and occasionally paradoxical accentuation of the background rhythm with eye opening [14].
Therapeutic measures include renal replacement therapy, with reversal of the symptoms and signs within days or weeks and renal transplantation, having the same beneficial effects. Correction of anemia with erythropoietin with target hemoglobin of 11-12g and of potential thiamine deficiency with B1 supplementation may also lead to cognitive improvement [14,17].

Pulmonary encephalopathy

This can occur in patients with chronic respiratory insufficiency frequently complicated by congestive heart failure and systemic or pulmonary infection. But it can also occur in more acute or chronic conditions, where from brain to muscle the neurorespiratory control of gas exchange is impaired. Brainstem lesions affecting the respiratory center, such as stroke, hemorrhage or compression, upper spinal cord injuries, polyneuropathies, such as Guillain-Barre syndrome or critical illness polyneuropathy, neuromuscular junction blockade, such in myasthenia gravis or Lambert-Eaton syndrome, myopathies affecting the diaphragms or intercostal muscles, are characteristic examples.
The pathophysiological basis is hypoxia and/or hypercapnea. As oxygen availability to the brain is decreased (decreased oxygenation, ventilation or hemoglobin carrying capacity, such as with carbon monoxide [CO] poisoning) or CO2 is increased, cerebral vasodilation ensues and cerebral blood flow increases, with ICP elevation. CO also affects the respiratory chain by binding to cytochrome c oxidase, worsening tissue hypoxia and creating deleterious reactive O2 species [18].
Although the clinical presentation of pulmonary encephalopathy may not differ from other types of delirium, occasionally papilledema is present if more chronic cases. Also a milder, indolent form, mainly with cognitive impairment only proven by neuropsychologic battery tests, may be present as in sleep apnea patients.
Additionally, CO poisoning may have a biphasic course. Initially symptoms of confusion, difficulty concentrating, dizziness, nausea, headache may present with 20-30% carboxy-hemoglobin (COHg) concentrations. Higher levels of COHg lead to ataxia, hallucinations, stupor and coma, with death usually occurring at levels of 80% or higher. Survivors who recover, 10-30% may develop extrapyramidal signs, memory loss, incontinence and psychotic behavior 3-240 days later. MRI in these delayed cases shows symmetrical bilateral putaminal or entire basal ganglia hyperintensities or symmetrical bilateral white matter changes in T2 with decreased ADC values (suggesting cytotoxic component) [14].

Treatment is administration of oxygen to correct the hypoxia, hyperbaric oxygen to enhance the elimination of COHg (from 4-5 hours to 20 minutes at 3 atmospheres; this treatment is still considered controversial) or invasive or non-invasive ventilation to improve the hypercarbia.

Posterior reversible leukoencephalopathy syndrome (PRES)

Initially was recognized in cases of eclampsia, severe hypertension and immunosuppression with cyclosporine after transplantation. However, many other conditions have been associated with PRES, including sepsis, systemic inflammatory response syndrome, renal or multiorgan failure, post-transplantation (bone-marrow or stem-cell, solid organs, graft-versus-host disease), drugs including immunosuppressants (cyclosporine A, FK-506 [Tacrolimus]), chemotherapy (cisplatin, cytarabine, tiazofurin, gemcitabin, bevacizumab [Avastin]), IVIG, autoimmune diseases (systemic lupus, scleroderma, Wegener's, ployarteritis nodosa), electrolyte derangements (hypomagnesemia, hypercalcemia, hypocholesterolemia) or hyperperfusion syndrome post CEA or during triple-H treatment for post-SAH vasospasm [14].

Clinically it presents with headache, nausea, vomiting, confusion or lethargy, seizures and visual disturbances. Hypertension is found in only 50-70% of cases. The lesions detected on MRI are in the majority parieto-occipital, but can also be more anterior in the frontal lobes or affect watershed or subcortical areas. Although the pathophysiology is controversial, the presence of vasogenic and occasionally cytotoxic edema has been explained by two opposing theories: hypertension with defective autoregulation (beyond the upper inflexion point of the curve) and hyperperfusion or endothelial injury, vasoconstriction and hypoperfusion [19].

The mainstay of treatment remains control of hypertension, removal of offending agents and treatment of underlying condition. In 25% the lesions are irreversible and the deficits persistent.

Alcohol withdrawal encephalopathy

Also known as delirium tremens, it can occur in 5-40% of patients admitted with alcohol dependence and still carries 15% mortality, if untreated. Initially, hyperactivity and tremulousness start within few hours after withdrawing from alcohol and peak after 10-30 hours. These signs can be followed by seizures (either generalized or focal, with onset 6-48 hours and peak 13-24 hours), auditory, visual or tactile hallucinations (onset 8-48 hours, duration 1-6 days) or delirium tremens (onset 60-96 hours) with severe autonomic hyperactivity.

Key treatment measures include fluid and electrolyte replacement (due to fever and diaphoresis, especially magnesium to avoid electrocardiographic QTc interval prolongation and torsades de pointes), thiamine supplementation (100 mg/day for 3

days) and benzodiazepines (either fixed dosing or symptom triggered regimens). For resistant cases propofol infusion or barbiturates can be used. Because intracranial hemorrhage is also prevalent in alcoholics, neuroimaging should be obtained for new-onset seizures, if the neurological exam confirms focality or if overt trauma is present.

Wernicke's encephalopathy

Wernicke's encephalopathy can result from alcoholism, but also from malnutrition, cancer, chemotherapy or liver or kidney disease. Inattentiveness, indifference, impaired memory, disorientation and disordered perception are common, but the most characteristic signs are from the eyes, including nystagmus, lateral rectus palsy (occasionally bilateral), conjugate horizontal gaze palsy or complete ophthalmoplegia. Truncal ataxia is present in 80% of patients and peripheral neuropathy is also common. The amnestic syndrome of Korsakoff's frequently emerges after the initiation of treatment and improvement of the acute Wernicke's signs. The ocular symptoms improve within few hours to days with thiamine 50-100 mg/day administration, but the ataxia less often.

Pancreatic encephalopathy (PE)

PE occurs in 1.7-35% of patients with acute pancreatitis. It begins within 2 weeks after acute pancreatitis, usually between day 2 to 5, and clinically does not differ from other encephalopathies. Although this entity remains controversial and many believe that is incorporated within the SAE spectrum (because many of these patients also have signs of sepsis or SIRS), others believe that it entails a different pathophysiology and potentially future treatment options [20].

More specifically, it has been hypothesized that levels of pancreatin (including trypsin, elastin enzyme, lipase and phospholipase A_2) enter the circulation, where activated PLA_2 transforms encephalin and lecithin into highly cytotoxic hemolytic encephalin and hemolytic lecithin. Both damage the blood-brain-barrier, dissolve the phospholipid structure of the cell membrane, hydrolyze mitochondria and cause demyelination and vasogenic edema. PLA_2 also passes through and has potent neurotropism, destroying the phospholipid layers of brain cells, and causing brain cell cytotoxic edema. Inflammatory cytokines, which increase after acute pancreatitis and also alter the permeability of the BBB, and systemic disturbances, such as hypoxia, hypotension, disseminated intravascular coagulopathy or fat embolism may also contribute to the delirium.

Interestingly there is no clear correlation between the severity of pancreatitis (amylase levels) and the incidence of PE. Higher lipase levels have been reported in the CSF of patients with PE, but this is rarely performed.

There is no specific treatment, only supportive plus thiamine supplementation to avoid development of Wernicke's after prolonged fasting.

Hashimoto's or corticosteroid-responsive encephalopathy

This uncommon syndrome is associated with high titers of antithyroid peroxidase (also known as antimicrosomal) or antithyroglobulin antibodies and is more common in women than men. However, the antibodies role in the pathogenesis of brain dysfunction is unclear, since they may also be circulating in asymptomatic patients. Other autoantibodies, including antineuronal and anti-enolase may play a more significant role, but this is unproven. Patients may have a relapsing-remitting course and present with tremor, stroke-like symptoms (transient aphasia), gait ataxia, seizures, myoclonus, sleep abnormalities, psychosis or a progressive cognitive decline [21]. The thyroid hormones and TSH may be normal, high or low. EEG shows diffuse slowing, triphasic waves or periodic lateralizing epileptiform discharges. Characteristically, these patients respond to corticosteroids, either IV methylprednisolone 1 g/day for 5 days or prednisone 60-100 mg/day for 10-30 days [21,22]. However, patients meeting all the above clinical and laboratory criteria for Hashimoto's without response to steroids have also been reported [21].

Hyponatremic encephalopathy

Acute drop of Na^+ (in hours) may lead to seizures or cerebral edema even with levels as high as 125 mEq/L, whereas more chronic Na^+ decrease (over days) even below 110 mEq/L can be better tolerated. Brain cells may initially develop edema as water enters into them, but later compensate to a normal cell volume by shedding solute followed by water to the extracellular space. In this chronic phase, if Na^+ is raised rapidly, the cells may shrink causing osmotic demyelination (previously known as central pontine myelinolysis), which can range from spasticity to locked-in syndrome to coma [23]. The treatment depends on the etiology. In hypertonic hyponatremia (due to presence of additional osmoles, such as mannitol or hyperglycemia), the treatment focuses on treating the underlying disorder with replacement of estimated salt losses. In hypovolemic hypotonic hyponatremia (from renal or cerebral salt wasting syndromes, gastrointenstinal losses, diuretics), normal saline should be given. In hypervolemic hypotonic hyponatremia (from congestive heart failure, ascites, nephrotic syndrome), free water restriction is instituted. In chronic isovolemic hypotonic hyponatremia (due to the syndrome of inappropriate secretion of antidiuretic hormone or hypothyroidism), water restriction and/or demeclocycline have a desirable effect, whereas in more acute situations 3% saline can be used at rates 1-2 ml/kg, with correction rate not more than 10 mEq/L/24 hours. If seizures occur, however, an initial faster correction rate (4-6 mEq/L within the first 6 hours) and if seizures stop, followed by a slower correction (i.e., up to 8-10 mEq/L/day) has been recommended. Newer vasopressin-2 antagonists may be used in hypervolemic or isovolemic hypotonic hyponatremias [24]

Hypoglycemic encephalopathy

Because of the brain dependence on glucose as its primary energy source, hypoglycemia (serum glucose < 40 mg/dL) may lead to serious sequelae. Depending on the baseline daily glucose levels, symptoms can occur at higher (diabetics) or lower (patients with very tight glycemic control) glucose levels than this [25]. Severe hypoglycemia can occur in Type 1 or Type 2 diabetics and most commonly is associated with insulin therapy (or sulfonylurea overdose in Type 2). In modern ICUs, the implementation of tighter glycemic control protocols has led to emergence of frequent hypoglycemic events and increased risk of death [26].

The neuroglucopenic symptoms and signs associated with either postprandial or fasting hypoglycemia are due to sympathetic system activation and secretion of catecholamines (cold perspiration, lightheadedness, tachycardia) and are followed by dysfunction of the nervous system (headache, confusion, tremor, stupor, seizures), which can be global or focal, mimicking stroke. When hypoglycemia becomes severe and prolonged, coma and decorticate or decerebrate posturing from selective brain damage occur, with some brain areas, such as the dentate gyrus of the medial temporal lobe, the superficial layers of the neocortex and the basal ganglia, being more susceptible to injury.

Treatment should be fast with administration of 50 ml of DW 50% IV, followed by DW 5% infusion. Glucagon administration although also effective may be underutilized [27].

Hyperglycemic encephalopathy

It can occur either in the context of diabetic ketoacidosis (DKA) or, more commonly, of nonketotic hyperosmolar hyperglycemia (NKH). Encephalopathy may occur at serum glucose levels > 300 mg/dL in DKA or > 600 mg/dL in NKH and the degree of impairment of consciousness may correlate with the degree of serum osmolality changes. Alterations in electrical activity within the ascending reticular activating system with multiple neurotransmitter derangements, as well as cerebral edema due to fast therapeutic interventions to correct hyperglycemia, have been implicated in the pathophysiology of the encephalopathy [14].

Neurologic symptoms and signs occur more frequently with NKH and progress from confusion and lethargy to stupor and coma. Focal neurologic deficits mimicking stroke or transient ischemic attack (hemiplegia, aphasia, speech arrest, visual changes) or hemichorea-hemiballismus can also occur with KNH [14]. Additionally, “reflex seizures” due to limb movement (even passive), then followed by refractory period, during which movement will not activate them can also be seen with NKH [28].

Treatment of the severely contracted volume with normal saline, IV insulin administration and correction of the profound electrolyte derangements usually improves the encephalopathy.

NMDA-receptor encephalopathy

This condition is caused by the presence of serum or CSF antibodies against brain N-methyl-D-aspartate receptors. Most patients are female (80%) and in most the presence of these antibodies should be considered paraneoplastic syndrome, because ovarian teratomas can be found in 26-59%. Only 2% of patients may have another type of tumor (neuroblastoma or Hodgkin's lymphoma [29]. However, there is another group of antibody-positive patients with encephalopathy without detection of neoplasms despite extensive evaluations (non-paraneoplastic syndrome) [30]. The younger the patient, the less chances a tumor will be found [29].

Symptoms and signs can be divided into a prodromal phase (headache, fever, vomiting, diarrhea), early phase after few days (with psychiatric symptomatology, such as anxiety, delusions, paranoia, echolalia or seizures) and late phase (where movement disorders, such as choreoathetoid, orofacial movements, myoclonic or oculogyric crises and opisthotonus or autonomic instability with hyperventilation, tachycardia, pyrexia or sialorrhea, predominate). Lower initial NMDAR antibody levels and less frequent confusion, agitation, amnesia and reduced consciousness may be found in non-paraneoplastic than paraneoplastic patients [30].

CSF may show initially lymphocytic pleocytosis, elevated protein and oligoclonal bands. Diagnosis is made when antibodies are detected in CSF or serum, although after treatment only CSF may remain positive. EEG may show diffuse or rhythmic delta activity or non-convulsive status epilepticus and MRI is non-diagnostic in the majority.
First step in treating these patients is removal of the teratoma if present. Subsequently, IVIG or plasma exchange or immunosuppression with methylprednisolone or rituximab plus cyclophosphamide will lead to improvement, but in 20-25% of patients recurrence will eventually mandate chronic immunosuppression [29].

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TABLE 1. Etiologies of metabolic encephalopathy. Modified from [1]

Legal and illegal drugs	Anticholinergics, antihistamines, tricyclic antidepressants, narcotics (especially meperidine), antibiotics (cefepime, imipenem, benzodiazepines, barbiturates, anesthetics, digitalis, corticosteroids, propranolol,, lithium, theophylline, H2-blockers, metronidazole, antiparkinsonian, antiepileptics, immunosuppressants (tacrolimus, cyclosporine, ifosfamide), recreational drugs (abuse or withdrawal), over-the-counter medications, herbal preparations
Toxins	Metals (Arsenic, Lead, Mercury), Ethylene glycol, methanol, cyanide, carbon monoxide
Metabolic	Liver failure, uremia, hypoglycemia, hyperglycemia, electrolyte abnormalities, hypercarbia, hypoxia
Endocrine	Thyroid, parathyroid, pituitary, adrenal gland dysfunction, uncontrolled diabetes, pancreatitis.
Neoplastic	Systemic cancer, paraneoplastic syndromes, CNS tumors, carcinomatous meningitis.
Nutritional	Thiamine, B12, niacin, folic acid deficiencies,
Miscellaneous	Severe anemia, dehydration, volume overload, burns, fat embolism, Chronic Obstructive Pulmonary Disease (COPD), migraine, posterior reversible leukoencephalopathy syndrome, sensory deprivation, sleep deprivation, Reye syndrome, idiopathic recurrent stupor (endozepine stupor)

TABLE 2. DSM-IV-TR Diagnostic criteria for delirium due to a general medical condition [31]

A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, to sustain, or to shift attention.
B. A change in cognition (such as memory deficit, disorientation, or language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.
C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
D. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.

TABLE 3. Laboratory investigation for metabolic encephalopathies. Modified from [1]

1. Complete blood count with differential, ESR and CRP
2. Serum electrolytes, BUN, creatinine, glucose.
3. Thyroid, parathyroid and adrenal hormone evaluation
4. Liver function tests, Amylase, Lipase, Ammonia
5. Troponin levels
6. HIV ELISA after patient's consent
7. Arterial blood gases with lactate level
8. Cerebrospinal fluid evaluation, including cytology.
9. Body fluid cultures (blood, urine, stool, sputum, CSF)
10. Culture of indwelling catheters.
11. Serum and urine toxicology, including antiepileptic drug levels or heavy metals

TABLE 4. West Haven Grading of hepatic encephalopathy [32]

Grade 1	Trivial lack of awareness
	Euphoria or anxiety
	Shortened attention span
	Impaired performance on addition
Grade 2	lethargy or apathy
	Minimal disorientation for time or place
	Subtle personality change
	Inappropriate behavior
	Impaired performance of subtraction
Grade 3	Somnolence to semistupor, but responsive to verbal stimuli
	Confusion
	Gross disorientation
Grade 4	Coma

METABOLIC ENCEPHALOPATHIES QUESTIONS

1. Delirium detection is based on
    a) Clinical suspicion, which is based on symptoms and signs
    b) Standardized scales such as the Confusion Assessment Method (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC), which guide towards specific etiologies
    c) Standardized scales such as the Confusion Assessment Method (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC), which are non-specific for etiology
    d) a) and c)
    e) a) and b)

2. Basic encephalopathy work-up includes
    a) CBC, electrolytes, glucose, ammonia levels, blood gases, CT of the head
    b) Lumbar puncture for NMDA-receptor antibodies in the CSF and MR spectroscopy
    c) Liver and pancreatic enzymes, thyroid function, tox screen, EEG
    d) a) and c)
    e) a), b) and c)

3. An 85 yo man is admitted to the Neuro-ICU post lumbar fusion. Three nights later he becomes agitated, confused, trying to get out of bed. When asked, he mentions that he has chest pain and an ECG is done showing sinus tachycardia with QTc interval of 500 msec. His wife mentioned that he is drinking whiskey daily. The best initial interventions are all EXCEPT
    a) Place the patient in a room with natural light
    b) Administer 10 mg of haloperidol and 7 mg of lorazepam IV over 5 minutes
    c) Check serum magnesium levels, start thiamine and folate and low-dose of lorazepam po or IV
    d) Perform a careful neurological exam and order a CT of the head if he has focal deficits
    e) Send urine for urinalysis and cultures& sensitivities, order a chest xRay and arterial blood gases

4. A 33 yo woman is admitted for acute liver failure due to acetaminophen overdose. She is drowsy and oriented to name and place. Her transaminases are in the 4-5,000 IU/L (normal < 40) range, ammonia level is 102 mcmol/L (normal 18-50), her INR is 3.2 and her head CT shows mild cortical edema but with open basilar cisterns. All are correct EXCEPT:
    a) She should be sent to the general ward after a psychiatric consult is completed to rule out suicidal ideation
    b) She should be kept in the ICU under close observation for worsening encephalopathy
    c) N-acetylcysteine infusion, ammonia lowering regimens and coagulopathy reversal interventions should be started
    d) If she eventually becomes stuporous, she will need to be intubated and mechanically ventilated and an ICP monitoring device should be placed after the coagulopathy is reversed
    e) Nephrology should be consulted for potential hepatorenal syndrome development and need for renal replacement therapy

5. In alcoholic patients
    a) Alcohol withdrawal seizures risk peaks during the first 24 hours after stopping drinking
    b) Delirium tremens onset is usually 2-4 days after stopping drinking
    c) Medial rectus palsy is the most common ocular sign of Wernicke's encephalopathy
    d) b) and c)
    e) a) and b)

6. Regarding Wernicke-Korsakoff's syndrome, all are WRONG except
    a) Korsakoff's amnesia is usually preceding the Wernicke's triad
    b) Wernicke's triad includes ataxia, sensory deficits and encephalopathy
    c) Alcoholism with thiamine deficiency is the only cause of Wernicke's encephalopathy
    d) Ataxia and cognition improve in all patients after institution of thiamine therapy
    e) MRI FLAIR changes in medial thalami, mammillary bodies, periaqueductal regions and midbrain tectum are characteristically found

7. Posterior reversible leukoencephalopathy syndrome (PRES)
    a) Is always associated with hypertension
    b) Should be treated with magnesium and lowering of blood pressure
    c) Can affect non-posterior areas of the brain
    d) Is always reversible, as the name implies
    e) Is only due to hypoperfusion and tissue ischemia, leading to reversible vasogenic edema

8. Regarding pancreatic encephalopathy
    a) It is a controversial entity and may co-exist with other encephalopathies, namely septic, hepatic or due to alcohol withdrawal
    b) There is no clear correlation between the severity of pancreatitis and the development of encephalopathy
    c) CSF lipase levels may be elevated in patients with pancreatic encephalopathy
    d) Pancreatic enzymes entering the circulation and affecting the blood brain barrier by lyzing cell membranes have been implicated in the pathogenesis of this encephalopathy
    e) All of the above

9. In Hashimoto's or steroid-responsive encephalopathy
    a) Circulating antiperoxidase (anti-microsomal) antibodies play a clear pathogenetic role
    b) Thyroid hormones are always high
    c) All patients with encephalopathy and high titers of these antibodies respond to corticosteroids
    d) All of the above
    e) None of the above

10. A 21 yo African American woman developed headache and fever, which in few days were followed by agitation and aggressive/violent behavior. She had two events witnessed only by her parents that seemed to be tonic-clonic seizures per description. Upon admission 10 days post onset, she is agitated with dystonic posturing, opisthotonus, tachycardia and profound sialorrhea. Diagnostic work-up should include
    a) Rabies antibodies, since the family mentioned presence of bats in the attic of their house
    b) An EEG to rule out non-convulsive seizures
    c) Serum and CSF titers of NMDA-receptor antibodies
    d) CT or MRI of abdomen-pelvis after a pregnancy test is found negative
    e) All of the above

METABOLIC ENCEPHALOPATHIES ANSWERS

1. **The correct answer is D.** These two scales cannot differentiate between hepatic or uremic or anoxic encephalopathies etc. They only confirm the presence of delirium.

2. **The correct answer is D.** Lumbar puncture with NMDA receptor antibodies and magnetic resonance spectroscopy are specialized tests, not widely available.

3. **The correct answer is B.** It would be prudent to measure and replace any magnesium deficits first to decrease the risk for torsades, and give smaller, incremental doses of lorazepam with careful monitoring of response.

4. **The correct answer is A.** Although a psychiatric evaluation may be useful to decide if she is a liver transplant candidate, patients with Grade 2 hepatic encephalopathy based on the West Haven grading system should be watched closely in an ICU environment for deterioration.

5. **The correct answer is E.** Lateral rectus palsy, often bilateral and nystagmus are the most common ocular signs of Wernicke's.

6. **The correct answer is E.** Wernicke's encephalopathy MRI findings are characteristically found in the medial mesencephalon and diencephalon.

7. **The correct answer is C.** PRES can affect frontal and subcortical or watershed areas, although parieto-occipital FLAIR changes on FLAIR MRI sequences is the most common.

8. **The correct answer is E.** All the above statements are true for pancreatic encephalopathy.

9. **The correct answer is E.** Other antibodies have been found in these patients. Also these antibodies are present in asymptomatic patients. Thyroid hormones and TSH may be normal, high or low. Several patients with these clinical and laboratory features do not respond to steroids.

10. **The correct answer is E.** Although sialorrhea is a rare but characteristic sign of NMDAR encephalopathy, rabies is in the differential diagnosis when it is present. Imaging studies may detect ovarian teratoma as the cause of NMDAR encephalopathy in a young woman.