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Managment of a Child With Decreased Level of Consciousness

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ABSTRACT

When a child presented with decreased level of consciousness in the emergency room, taking the right approach is one of the most important skills that every emergency physician should have. Ideally, there should be a defined diagnostic and therapeutic algorithm in the emergency room for managing these children in order to minimize difficulties diagnostically and maximize time spent helping the child. This article describes the history-taking, and physical and neurologic exams the affected child should be assessed with and explains the potential etiologies of a decreased level of consciousness. These factors are classified into traumatic and non-traumatic agents. Infectious causes of encephalopathy and the applied classification of them has been emphasized.

Keywords: Unconsciousness; Coma; Encephalopathy; Child

1. Introduction

Awakening (arousal state) and consciousness (awareness state) are two complementary concepts of consciousness. A healthy relationship between networked systems of ascending reticular activating system (ARAS) with higher centers such as the hypothalamus, thalamus and cortex of brain regulate and differentiate between arousal state versus asleep state. The ascending activation system consists of a network of distributed and decentralized neurons located in the medulla oblongata and are drawn to the midbrain and diencephalon (1).

Awareness versus disorientation is due to a proper contact of cortex with the sub cortical structures, leading to an awareness of time, place and person, therefore impaired consciousness is the result of functional or structural abnormality of brain stem or bilateral lesions of brain hemispheres. This means that only lesions of the brain can lead to impaired consciousness that are either bilateral hemispheric or in the brain stem (2).

Decreased levels of consciousness depend on the severity of central nervous system dysfunction and can be divided into the following steps:

- Obtundation: A condition in which the patient is confused and without full knowledge of the time, place and person, but is awake.
- Lethargy: A state in which the patient has, in addition to reduce the environmental awareness, automati-

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Implication for health policy/practice/research/medical education:
The algorithm is essential for health decision in emergent cases and it has high burden. There are diversity in management.

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cally goes to sleep, but is awakened by sound stimuli and sleeps again.

• Stupor: A condition in which the patient is in deeper levels of unconsciousness, but only responds to painful stimuli.

• Coma: A condition in which patient's level of unconsciousness is so deep that does not respond to even painful stimuli.

In addition, delirium has to be mentioned as a condition with not only loss of attention and confusion, but also violent excitement or emotion which can progress to coma. Delirium can be seen in children with poison or drug intoxication (3). A coma is a life threatening state that requires immediate emergency intervention. The prognosis of coma can be variable. Some improve with increasing awareness, while others sustain a loss of consciousness as Persistent Vegetative State (PVS) or deteriorate to death (4). The criteria for determining a patient's level of consciousness, GCS (Glasgow Coma Scale), is a practical measure which scores in terms of three parameters: open the eyes, voice response to stimuli, and motor response to stimuli. Pediatric GCS criteria or PGCS is usually used for younger kids (mostly under 2 years). The GCS score ranges between 3 to 15. If the score over 13, this usually means mild brain dysfunction, if the score is located between 9 to 12 this usually means moderate dysfunction and that equal or less than 8 means severe brain dysfunction (*Table 1*).

Table 1. Coma Scale Glasgow (GCS), Pediatric Coma Scale Glasgow (PGCS) Scores

Rating Criteria	GCS	PGCS	Score
Openeyes			
	Spontaneous	Spontaneous	4
	In response to commands	To Sound	3
	To painful stimuli	To painful stimuli	2
	No Response	No Response	1
Audio responses to stimuli			
	Oriented	Produce sound appropriate to age	5
	Confusion, disoriented	Crying and restlessness	4
	Inappropriate words	Cries in response to painful stimuli	3
	Incomprehensible sounds	Sighs in response to painful stimuli	2
	No sound	No sound	1
Motor responsesto stimuli			
	Obey the commands	Spontaneous movements	6
	Localize in response to painful stimuli	Drag in response to tactile stimuli	5
	Withdraw in response to the painful stimuli	Withdraw in response to the painful stimuli	4
	Abnormal flexion in response to painful stimuli (Decorticate)	Abnormal flexion in response to painful stimuli	3
	Abnormal extension in response to painful stimuli (Decerebrate)	Abnormal extension in response to painful stimuli	2
	No response	No response	1

2. Causes of Decreased Level of Consciousness

Causes of decreased level of consciousness and coma in children eventually grow into traumatic and non-traumatic categories. Non-traumatic causes are usually happened in younger and traumatic in older children, particularly teenagers. The prevalence of these categories are almost the same and about 30 in every 100,000 children are referred to the hospitals (5). The most common causes of non-traumatic coma are: infections, toxins, status epilepticus, cardiac or brain abnormalities, hypoxia or ischemia and metabolic disorders, consecutively. According to a study, the causes of decreased level of consciousness are infectious diseases (60%), toxins (19%), status epilepticus (10%), intracerebral hemorrhage (7%), and miscellaneous (4%), in order (6).

In another study of 150 cases of children with non-traumatic coma, the causes were as follows:

• Infections (7.32%), including meningitis, encephalitis, systemic infection,

• Status epilepticus (4.29%),

• Metabolic disorders including diabetes ketoacidosis (3.7%),

• Poisoning (7.6%),

• Accident with hypoxic injuries such as drowning,

electric shock and suffocation (6%),

• Brain shunt dysfunction (9.4%),

• Miscellaneous (3.7%) including acute disseminated encephalomyelitis (ADEM), vasculitis and hypertension encephalopathy,

• Unknown (5%)

In this study the infectious causes were more common in children under 2 years old and toxic causes were the case mainly between 2 and 6 years old. Infectious causes and poisoning are the most common causes of death in children (7).

Therefore, when facing a child with consciousness abnormality not due to trauma and especially with fever, infectious causes such as meningitis, encephalitis, post infectious encephalopathy and rare infectious causes such as tuberculosis meningitis and brain malaria should be considered.

Infections tend to be more common and are treatable so the doctor should always consider this first as a causal agent. Other causes of coma in children to be investigated are the two categories of structural abnormalities such as hemorrhage, hydrocephalus, abscesses, tumors, thrombi and cerebral infarction, and non structural ones such as toxins, infections, metabolic causes and seizures (7).

Taking a precise history is the first and main step in order to find the cause for the lack of consciousness. In the case of trauma, intracranial hemorrhage or microscopic injuries like concussion are the most important causes to check. Typically, abrupt consciousness abnormality in a previous healthy child means intracranial hemorrhage with or without trauma, seizure, cardiac arrhythmia or intoxication. A more gradual course of unconsciousness is associated with infections, metabolic causes or intracranial masses (space occupying lesions). A history of headaches, nausea, blurred vision preceding loss of consciousness, raises the issue of increased intracranial pressure. Previous underlying diseases such as diabetes, hypoglycemia or ketoacidosis may also be considered. Congenital metabolic diseases are possible for patients with a history of previous attacks (8).

3. Clinical Examination

After taking the history, the second main step in evaluating a child with decreased level of consciousness is a vital sign assessment and establishing ABCD, as a matter of principle. The following major examinations should be performed:

• Temperature: Differential diagnosis of fever and decreased level of consciousness are infectious, inflammatory disorders, heatstroke-induced hyperthermia, malignant neuroleptic syndrome, status epilepticus, hyperthyroidism and some toxic poisoning with anticholinergic agents. Infectious causes, some drug poisoning, and hypothyroidism should be considered if there is hypothermia, particularly in small infants (9).

• Heart rate: There is tachycardia in patients with fever, different causes of shock, such as hypovolemic, septic or cardiogenic shock (cardiomyopathy or arrhythmias) and non-convulsive status epilepticus. Bradycardia in cases of hypoxemia (because of the effect on myocardial tissue) and increased intracranial pressure (ICP) as one component of the Cushing's triad phenomenon (bradycardia, hypertension, abnormal pattern of respiration) can be seen. This triad is seen in only 10% of the cases of increased ICP (9).

• Number and pattern of breathing: Tachypnea can be seen in a child with infectious causes of decreased level of consciousness, such as sepsis, hypoxemia, metabolic disorders and occasionally presence of pain. In addition to respiratory rate, an abnormal breathing pattern is also very important. Deep and rapid breathing (hyperventilation) is seen in patients with brain edema and diabetic ketoacidosis. Hyperpneas alternating apnea periodic breathing (Cheyne Stokes respiration) or irregular breathing, unpredictable (ataxic breathing) are common in brain damage. Occasionally breathing with prolonged apnea (apneaostic breathing) exists.

• Blood pressure: Hypotension in a child with a decreased level of consciousness indicates shock, acute adrenal insufficiency, or toxicity. Severe hypotension can cause decrease cerebral perfusion and even trigger irreversible damage to neurons (10). Hypertension can also be seen with increased intracranial pressure, renal failure, poisoning or severe pain. High blood pressure alone can cause loss of consciousness and even coma, hypertension encephalopathy.

• Examination of the skin and mucosa: Changing of skin color to blue (hypoxia) or pink (carbon monoxide poisoning), jaundice and pallor (anemia) in patients with a decreased level of consciousness can be meaningful. Bleeding lesions such as purpura, and ecchymosis indicate serious infections, especially septicemia. Head trauma should be considered if there is any bruising on the skin, around the eyes (raccoon eyes), on the mastoid area (battle sign), runny nose or ears due to CSF fluid from the nose (rhinorrhea) or ear (otorrhea) are issued (10).

• Fundoscopy: Funduscopy is very important in every person with a decreased level of consciousness. Presence of papilledema, usually following hours of increased ICP can be seen (11) and the presence of retinal hemorrhages in an infant indicates “shaken baby syndrome”.

• Meningeal irritation: Meningial irritation signs such as neck stiffness may be absent in a child with deep coma and intracranial infections like meningitis and subarachnoid hemorrhage. Therefore meningitis cannot be ruled out in their absence (12).

4. Neurological Examinations

Neurological examinations cannot be performed in ordinary way in a child with decreased level of consciousness. Impaired neurological examination of the child includes the following three steps:

1) The child's level of consciousness: As was mentioned previously, GCS or PGCS are essential elements when assessing the consciousness in a child and assist to determine the prognosis of the disease in children.

2) Evaluation of the motor system in children: Assessment of patient's motor system consists of three components: muscle tone, spontaneous or stimuli triggered movements, and deep tendon reflexes (DTR). Muscle tone is evident by posture or position, hypotonia or hypertonia. Spontaneous and targeted movements mean lighter degree of loss of consciousness. Increase or decrease DTR has to be determined in this situation.

3) Determination of brain stem reflexes: Brain stem reflexes included pupillary reflex, corneal reflex, and extra-ocular reflex describes as below:

A) Pupillary reflex: Pupillary response to light stimulation involves second cranial nerve (optic nerve) as afferent nerves to midbrain and third cranial nerve as efferent nerves to circular muscles of iris. Parasympathetic stimulation causes contraction of the muscles (Miosis) and sympathetic stimulation causes muscle relaxation (Mydriasis). Abnormal reflex means problems in the reflex pathway including the optic nerve, midbrain or oculomotor nerve. Anisocoria (asymmetry in pupils size) is due to mydriatic drug dispensing (hematropin), cranial base lesions, supratentorial lesions or pressure on the third cranial nerve or its nucleus. Miotic pupils are seen in opium poisoning or such traumas that cause pons hemorrhage (11).

B) Corneal reflex: A corneal stimulus causes closing the eyes spontaneously. It is controlled by fifth and seventh cranial nerves and midbrain.

C) Extra ocular reflexes: Eye movement is controlled by third, fourth and sixth cranial nerves. Coordinated eye movements in a child with a decreased level of consciousness, means intact pons. Doll's eye reflex and caloric test are considered as significant reflexes of eye movements.

1. Doll's eye reflex: In motion of the head to one side, eyes normally go to the contralateral side (doll's eye). Lack of this reflex means lesion of pons, the nerves involved in eye movements, metabolic deep coma or sometimes drug poisoning.

2. Caloric reflex (oculovestibular reflex): If the eardrum is intact, pouring cold water (about 10 to 30 cc in the case that the head is elevated 30 degrees) in the patient's ear can cause nystagmus movements to the contralateral ear (fast phase). Warm water directs this phase of movement to the ipsilateral ear. Absence of eye movements in this test means pons lesions (11).

The next step is providing the list of problems and consider diagnosis accordingly. If no specific diagnosis is probable according to the problems list, then laboratory tests should be requested.

5. Laboratory Tests

In the case of a child with decreased level of consciousness, specific laboratory tests are required according to the findings. If there are no specific clues in history or physical exams, core tests should be requested urgently in order to conduct to either specific diagnosis or more sophisticated tests or interventions. These core tests would be blood sugar, creatinin, urea and electrolytes, including serum sodium, potassium, chloride and calcium, peripheral blood cell count and differentials, urinalysis testing and blood cultures, liver function tests, arterial blood gas, and serum ammonia.

Following the above tests, it is recommended to store and freeze 2 cc of patient plasma and about 10 cc of urine for future testing. Blood glucose monitoring is recommended in all patients with a glucometer at first and then more routine tests are confirmed as hypoglycemia and hyperglycemia with ketoacidosis are treatable emergency causes of impaired consciousness in children. Delay in their management causes irreversible damage to the brain (11).

It is recommended to use arterial specimen for ammonia test that kept not more than 15 minutes in the room temperature. The plasma should be separated as soon as possible, unless keeping with ice pack. Inherited and acquired metabolic causes are usually considered, if the serum ammonia is too high. Hereditary metabolic causes include disorders of the urea cycle, organic acidemia, the oxidation of fatty acids and acquired causes are acute renal failure, chronic liver disease, urinary tract infection with urease-producing agents, gastrointestinal bleeding, RTA type I, Reye syndrome, and taking some drugs such as sodium valproate should be considered. Measurement of serum lactate is recommended in the case of metabolic acidosis found in blood gas assay. In addition to acquired causes, inherited metabolic disorders such as disorders of the urea cycle, organic acidemia, the oxidation of fatty acids and mitochondrial enzymes are considered at this point. Other essential interventions are as follows:

a. Chest x-ray is requested in all patients especially those with probable respiratory tract involvement or those with possible aspiration pneumonia and particularly following intubation. Abnormal CXR in these patients suggests: aspiration pneumonia, septic pulmonary emboli and endocarditis, TB, fungal pneumonia, mycoplasma pneumonia, amibiasis cysts, metastaic lesions and vasculitis.

b. Neuroimaging: Brain CT scan without contrast is considered as first choice in cases of head, trauma or

probable CNS involvement with fever, papillary edema or focal neurological signs or for ruling out life threatening causes such as brain herniation, hydrocephaly or presence of cerebral edema signs or brain occupying lesions including brain tumors and abscesses. MRI is usually indicated in the next step to see more details about brain parenchyma such as encephalitis, diffuse axonal injuries, hemorrhage, cerebral venous thrombi and demyelization lesions, especially in inferatentorial injuries (13).

c. Lumbar punction is not recommended when GCS is equal or less than 12, unless it is proved to be harmless according to the brain CT scan (14). However, despite a normal CT scan, the possibility of brain herniation following LP cannot be ruled out (15). Thus, it is recommended that when there is a risk of brain herniation, LP should be delayed for 24-48 hours even if the CT scan is normal. However until performing LP in any clinical suspicion of infection within the brain, the patient should be treated with antibiotics for bacterial meningitis and encephalitis caused by herpes simplex (16). The delayed LP for 24 to 48 hours, does not affect the CSF analysis except the CSF culture (17).

d. Electroencephalography (EEG) should be obtained in patients with deep coma without apparent etiology as non convulsive status epilepticus can be a cause of non-traumatic coma in children. In addition, EEG is beneficial in areas other than convulsive findings in EEG, such as slow rhythm or asymmetry.

6. Encephalopathy and Its Variants

Encephalopathy is defined as a condition in which the brain integrated abnormalities cause changes in consciousness, seizures or behavioral changes without structural factors, such as brain tumor or hemorrhage as their causes. Encephalopathy in children is reversible but it is a life threatening condition that requires emergency diagnosis and intervention. Pathogenic mechanisms of encephalopathy would be inadequate blood flow and oxygen and glucose supply to the brain, endotoxins and exotoxins in the brain blood flow that injure brain, cerebral edema and increased ICP, which decrease blood flow to the brain, and increased cerebrospinal barrier (BBB) permeability in encephalopathy.

6.1. Major Causes of Acute Encephalopathy in Children

- Hypoxic ischemic encephalopathy, which is usually followed by injuries such as choking, drowning and other causes like trauma, cardiac arrhythmia or monoxide gas poisoning. The duration and severity of hypoxia determines the severity of brain damage.

- Metabolic encephalopathy: The common causes of metabolic encephalopathy are hypoglycemia and ketoacidosis. Hypoglycemia is reversible but can cause serious damage and should be considered initially in cases that there is no identified cause for decreased level of consciousness. The most common and imperative causes of hypoglycemia in children are ketotic hypoglycemia, excessive insulin usage, hepatitis, metabolic diseases such as a glycogen storage disease (GSD), glucoconeogenesis disorders, and disorders of fatty acids metabolism and less common causes are growth hormone or cortisol deficiency, Reye syndrome and hyperinsulinemia. One of the other causes of metabolic encephalopathy in children is sudden changes in blood osmotic pressure (more than 330 or less than 260 mmol per liter), which can be associated with hypernatremia, hyponatremia, hypocalcemia or hypercalcemia (18).

- Encephalopathy due to organ failure: Liver failure, either acute or chronic, can cause hepatic encephalopathy as toxic metabolites such as ammonia are produced, or cerebral edema and brain perfusion abnormalities can be ensued. Uremic encephalopathy in renal failure is due to toxic metabolites such as creatinin, guanidine, free oxygen radicals or parathormone. The severity of signs does not necessarily correlate with blood urea level. Sometimes encephalopathy is occurred in patients following dialysis or dialysis disequilibrium syndrome simply named as DDS.

- Congenital metabolic encephalopathy: Encephalopathy in some congenital metabolic diseases is presented following stress or infections. There may be repeated attacks of encephalopathy in the patient's record. Some of the metabolic disorders such as organic acidopathies, amino acidopathies, the disorder of urea cycle, metabolic disorders of carbohydrates and fatty acid oxidation disorders mimic recurrent Reye-like syndrome.

- Encephalopathy due to drugs and toxins: lead and some toxins, some medications, including tricyclic antidepressants, benzodiazepines and phenobarbital can be associated with encephalopathy.

6.2. Assessment and Differential Diagnosis of Acute Infectious Encephalopathy in Children

Acute encephalopathy typically presents with altered level of consciousness in a child and is considered a medical emergency that can be with or without focal neurological signs. Most common etiologies of acute encephalopathy in children are infections, metabolic disorders, cerebral hypoxemia or ischemia, intoxications or space occupying lesions. Acute or recent infections are the most common cause called "infection associated encephalopathy". Infection cause encephalopathy by either direct invasion of brain (the infectious agent can be isolated from brain parenchyma or CSF) or indirectly affect CNS, in conditions like ADEM (19) (*Table 2*).

Table 2. Infection Associated Encephalopathy

Mechanism	Examples
Direct invasion of brain tissue by infectious agents	Acute Encephalopathies
Indirect invasion of brain tissue by infectious agents	Immune mediated Encephalopathies: ADEM, AHLE
	Acute toxic encephalopathy: ANEC, Reye syndrome, Ekiri syndrome
	Septic encephalopathy

Abbreviations: ADEM, acute demyelization encephalomyelitis; AHLE, acute hemorrhagic leukoencephalopathy; ANEC, acute necrotizing encephalopathy of childhood

-Acute Encephalitis: Encephalitis, or inflammation of the brain parenchyma resulted from direct invasion of infectious agents into brain, mainly affects gray matter of the brain. Perivascular inflammation, nerve damage, neurophagia and necrosis of tissue are main pathologic characteristic of the disease (19). Fever, seizures and acute altered consciousness for at least 8 hours are characteristic signs of the disease (20). In addition, the organism responsible for the disease can be isolated from brain tissue. Among causes of encephalitis in children, viruses are the most common which include *Herpes simplex virus* (HSV), *Varicella zoster* (VZV), *Epstein-Barr* (EBV), *Cytomegalovirus* (CMV), *HHV 6* and 7, *Enterovirus, Adenovirus, Influenza virus* types A and B and *Arbo viruses* (such as the *Japaniess Encephalitis Virus, West Nile virus* (WNV), *Dengue virus*). Bacterial agents, ricketsia, fungi and protozoa should be considered too. Important non-viral causes are, *Mycoplasma pneumonia, Mycobacteria tuberculosis* and *Brucella*.

Accurate history of recent travel to endemic areas, (Japanese encephalitis due to travel to South East Asia or Central Africa), the season (*Enteroviruses* common in summer and autumn), contact with animals (rabies and brucellosis) and probable immunodeficiency such as HIV infection (CMV encephalitis) infection are valuable in reaching the diagnosis.

Neuroimaging of the brain, especially MRI is the method of choice to differentiate ADEM in suspected cases. EEG, or electroencephalogram, is a diagnostic tool in patients with suspected encephalitis. EEG not only detects non convulsive status epilepticus but also some kinds of encephalitis, such as herpes encephalitis with PLED changes (21).

CSF patterns is similar to aseptic meningitis which mainly include, pleocytosis (10-500 cell/mL), mild or moderate increase in protein (40-150 mg/mL) and normal glucose (CSF glucose to blood glucose ratio at above 50%). The lack of pleocytosis in some cases of Herpes encephalitis, especially in the early days is seen.

Positive CSF culture, or PCR can be seen in patients with encephalitis. Nowadays, PCR technique due to its high sensitivity, specificity and fast response is the method of choice for viral encephalitis in children.

Serology for detection of IgM antibody has restricted indication in children for its delayed rises and low specificity for detection of the cause of encephalitis (increased IgM reveals acute infection, but not necessarily encephalitis). In addition, reactivation of virus does not rise IgM in some cases. Brain biopsy used to be the gold standard in diagnosis prior to PCR became applied commonly, but as an invasive technique, it is not used routinely.

One of the most important and treatable encephalitis in children is encephalitis due to Herpes viruses such as HSV that can be treated with intravenous acyclovir for 2-3 weeks (22, 23). In patients with a low prior probability of HSV encephalitis (normal neuroimaging, less than 5 cells/mm2 in CSF, normal mental status), a negative CSF HSV PCR result reduces the likelihood of disease to less than 1 percent. Acyclovir therapy should not be discontinued on the basis of a negative CSF PCR obtained less than 72 hours after onset of symptoms for patients in whom there is high suspicion of the clinical suspicion of HSV encephalitis. (Despite these concerns, false negatives are fewer than 0.4%, examples of HSE missed by PCR) (24). The duration of treatment is shorter in VZV encephalitis (7-10 days) (25). The mentioned treatment decreased mortality in HSV encephalitis from 70% to 20% (26). Other antintiviral drugs such as Ganciclovir (CMV encephalitis), Oseltamivir (Influenza encephalitis), Pleconaril (Enterovirus encephalitis) and Ribavirin (WNV encephalitis) are also used. In a special circumstance, early administration of aniviral is the key point for decrease mortality in viral encephalitis.

-ADEM (Acute Disseminated Encephalomyelitis): It is a kind of inflammatory encephalopathy in children, that is multifocal and involves brain white matter (sub-cortical), predominantly. It typically occurs following a viral infection in the past few weeks. In contrast to Multiple Sclerosis (MS), ADEM is monophasic.

Lymphocytic inflammatory cell infiltration with demyelization and infarction are seen in pathological surveys of specimens (27). There is a variation of disease, known as AHLE or acute hemorrhagic leukoencephalopathy, with necrotizing vasculitis of small vessels seen in microscopic view. AHLE is more lethal in comparison with ADEM that is more common

form. They are considered to be autoimmune and recent viral infections or vaccinations are provoking factors for their presentation. The duration between infection and presentation of disease is usually 4-21 days (for example in *Mycoplasma pneumonia*), but it is shorter in AHLE (28, 29). Clinical presentation of ADEM vary depending on the regions of brain involved. It can even be seen as a single focal involvement. Demyelization of both CNS and PNS is rarely ever seen together. The seizures are infrequent and unlike AHLE systemic symptoms are less common. MRI can differentiate ADEM, AHLE and other encephalopathies. Increase in white matter signal is seen in ADEM, unlike MS with predominantly gray matter involvement. Lesions are not usually seen in brain CT scan in the first 4 to 5 days of onset of symptoms (30).

Lymphocytic pleocytosis is commonly seen in the CSF of patients with ADEM, while increasing PMN and RBC are usually combined in AHLE. Increased protein in the CSF is seen in both. Increased CSF monoclonal IgG in patients with ADEM have been reported (incidence of 0 to 58%), while this phenomenon is rare in the AHLE (31).

CBC includes neutrophilia and lymphopenia in some cases of ADEM, but generally, it is not helpful, whereas in systemic disorders like AHLE, leukocytosis, polynucleosis, increased atypical lymphocytes, elevated ESR and albuminuria are seen (29).

These two syndromes are treated by immunomodulator drugs. Pulse therapy with corticosteroids for 3 to 5 days is usually the first option. In refractory cases, IVIG or plasmapheresis could be applied. AHLE has very high mortality in comparison with ADEM even with treatment and it reaches about 70% (29).

-ATE (Acute Toxic Encephalopathy): These are caused by both infectious (Reye' syndrome, Ekiri) and non infectious causes. The characteristic feature of them is cerebral edema, with some evidence of inflammatory cells infiltration in the CNS. It seems that an infectious trigger produces a progressive pathologic processes results in brain edema with predominant impairment of brain cells mitochondrial function. Reye's syndrome which can be seen in some congenital metabolic disorders has characteristic features of hyper ammonia, lactic acidosis and hypoglycemia. It is caused by brain and liver cells mitochondrial dysfunction resulting in fatty degeneration changes of tissue and pleomorphic changes of neural cell mitochondria (32).

Similar changes in the mitochondria of neurons are seen in children with ANEC and Ekiri syndrome (33, 34). Reye's syndrome in children presents typically, following Influenza A or chicken pox infection and usually following consumption of aspirin. While infectious causes of ANEC syndrome are numerous, Ekiri's syndrome typically occurs after Shigella infection. Its neurological symptoms are similar to Reye's syndrome.

Cerebral edema, increased ICP and lack of pleocytosis are characteristic features of these syndromes. The only significant change in CSF is increased protein. ATE diseases occur mainly in children younger than two years old age. Although they have been reported later in the life too (35). Fever, headache, malaise, vomiting, and seizures are common symptoms of the disease and local findings may also be seen due to increased intra cranial pressure.

In ANEC Syndrome, despite an increase in liver enzymes similar to Reye's syndrome, hyperammonia and hypoglycemia are uncommon. Unlike Reye's syndrome, ANEC is characterized by necrotizing and signal changes of thalamus seen on MRI with contrast. These changes and similar lesions elsewhere in the CNS can cause local symptoms in children. In these patients, multiple and symmetrical lesions are seen in the thalamus, putamen, brain white matter, cerebellum and brain basal tegmentum. ANEC has fulminant course with early seizures, impaired consciousness, vomiting and varying degrees of liver dysfunction, lead to severe brain damage or death. Edema, diffuse hemorrhage and necrosis are seen in the pathologic view. Absence of inflammatory cells in the brain parenchyma differentiate the disease from ADEM and acute encephalitis. Another name for the disease is infantile bilateral thalamic necrosis.

There is no specific treatment for this syndrome. It has very high morbidity and mortality (29). Maintenance therapy is usually the only recommended treatment includes reducing ICP, correction of serum glucose and electrolytes.

- Septic Encephalopathy: This kind of encephalopathy is a common cause of infection associated encephalopathy in children which occurs in 50-70% of cases following septicemia. There are no specific diagnostic tests. Actually it is due to increase serum levels of inflammatory mediators such as:

Interferon alpha, interleukin-I and tumor necrotizing factor alpha, and their impact on CNS neurons. Aromatic amino acids or false neurotransmitters in these patients enter the CNS due to the high permeability of the BBB and cause symptoms of disease include decreased mental activity, attention deficit, disorientation, delirium and coma (36). Diagnosis is by exclusion of other causes. The neurological findings are usually symmetrical and CSF has slightly increased protein but no other abnormal findings. Treatment and prognosis are dependent on etiologies of septicemia and mortality is usually high. *Table 3* describes the important points in different forms of infection associated encephalopathies.

Table 3. The Important Points in Different Forms of Infection Associated Encephalopathies.

Encephalopathy	ATE	ADEM	Acute Encephalitis	Septic Encephalopathy
Age	Less than 2 years	More than 2 years	All ages	All ages
Prior infection	Yes	Yes	Yes/No	Yes
Fever	Common	Variable	Common	Present
Seizure	Common	Rare	Common	Common
Signs of meningeal irritation	No	Sometimes	Sometimes	Common
Focal neurological symptoms	Yes/No	Yes/No	Yes/No	No
Increased CSF pressure	Yes	Yes	Yes	No
CSF pleocytosis	No	Yes	Yes	No
Increased CSF protein	Yes	Yes	Yes	No
Positive PCR in CSF	No	No	Yes	No
MRI findings	Diffuse brain edema	Diffuse lesions in the white matter	Diffuse inflammatory lesions	Non-significant
Histological findings	Brain edema without inflammatory cell infiltration	Perivascular inflammation associated with demyelization	Perivascular inflammation associated with neuronal damage	Non-significant

Abbreviations: ADEM, acute demyelization encephalomyelitis; ATE, acute toxic encephalopathy

7. Trauma: an Important Cause of Loss of Consciousness

Head trauma is an important cause of coma in children and may have serious damages especially in children less than 2 years old or those who fall from altitude higher than one meter (37). It can cause concussion, which can be associated with impaired consciousness that last less than 24 hours, vertigo, headache, nausea and vomiting, blurred vision and memory loss. Brain CT scan is unnecessary, unless there is persistent or focal neurological deficit.

Post trauma concussion can be divided into three types according to severity and duration of symptoms:

-Grade I: A condition without loss of consciousness and the symptoms last less than 15 minutes. No intervention is required.

-Grade II: In this condition consciousness is preserved, but symptoms last more than 15 minutes. Brain CT scan is not required but patient should be under observation.

- Grade III: Loss of consciousness presents and symptoms lasting more than 15 minutes. Brain CT scan and advanced survey are usually required.

Children with brain injury, but preserved level of consciousness and normal neurologic examination whose parents are reliable, can be discharged with information about warning signs.

Black out is a temporary loss of consciousness that may be created due to impaired brain blood flow (fainting), dysfunction of brain cells (after seizures) or a mental disorder (psychological).

On the other hands, the study revealed that syncope is a common phenomenon in children. About 20% of children up to the age of 15 have experienced an episode of syncope (38). It is a temporary, reversible loss of consciousness due to brain transient hypo perfusion. One of the most common causes of syncope in children is a benign phenomenon called vasovagal syncope. Another cause is prolonged QT syndrome which should be considered in case of repeated attacks of syncope and is diagnosed with ECG monitoring and Tilt test.

TIA (Transient Ischemic Attack) which unlike black out, is a loss of consciousness associated with transient neurologic symptoms such as hemiplegia, and usually clears up in less than 24 hours. In these cases, the patient is likely to have vascular lesions.

There are three states that must always be distinguished from coma and are as follows:

- Locked out state: It is due to acute brain stem especially pons lesion and presents with palatal paralysis and disorders in movement and speaking, but preserved consciousness and the ability of blinking and voluntary eye movement. Paralysis due to Guillain-barre syndrome or botulism may mimic this state.

- Abulia or Mutism is due to frontal lobe lesions. The patient, remains conscious and can follow objects with the eyes but cannot follow the motion commands.

- Catatonia: It is a psychological disorder of most adolescents with unresponsiveness to ordinary stimuli, but a preserved response to painful stimuli and ability to keep body posture even in upright position.

8. Management of Patients With a Decreased Level of Consciousness

The initial treatment of these patients is generally supportive till the etiology is specified. The first objective is to minimize impaired brain perfusion that is achieved by proper oxygenation, fluid and electrolyte administration and monitoring vital signs.

Following stabilizing the patient's vital signs, medications with potential toxicity should be discontinued.

If possible, the patient should be transferred to the intensive care unit. In cases of GCS less than or equal to 8, intubate child to maintain appropriate airway and prevent aspiration. Consider neck immobilization with brace in cases of probable spinal injury. Glucose should be administered 2.5 cc/kg of 10% glucose after obtaining a blood sample. In the next phase, the experimental treatment for potentially dangerous causes such as hypoglycemia, increased ICP, bacterial meningitis or viral encephalitis (herpes) should be performed.

In the case of probable increased ICP, the following interventions are recommended:

Reduce fever, and stop shivering, raise the child head as much as 30 degrees from the ground, keep moderate hyperventilation (PCo2 to be between 30 to 35 mmHg), and finally administer mannitol (0.25-1) mg per kg of body weight and repeat it if necessary and there is not any contraindication. Neurosurgical consultation should be obtained.

In case of non convulsive seizure, phenytoin 15-20 mg/kg or lorazepam 1-2 mg injected slowly, are recommended.

Electrolyte disorders in children can cause coma or be its consequences. Therefore administration of isotonic fluids (normal saline or Ringer's lactate) in these children is recommended.

In probable and suspected cases of intoxication, it is recommended to be given antidote, such as 1-2 mg naloxone in cases of poisoning by opium (opium) or flumazenile in cases of poisoning with benzodiazepines. This latter should be used with caution in cases of seizure. Gastric lavage with activated charcoal to reduce absorption of toxic materials is recommended.

Prescription of tranquilizers because of relative difficulty in the monitoring of the patient's general and neurological examination, hyperventilation or hypotension is not recommended if possible.

Brain herniation (Transtentorial herniation), as a danger sign in physical examination and neuroimaging should always be in mind, which is usually followed by a sudden increase in ICP with an open or closed fontanel. It is divided into central or lateral (uncal) brain herniation. Uncal herniation occurs when temporal regions of the brain herniate. It is usually asymmetric and presents with third cranial nerve palsy and subsequent hemiplegia due to unilateral pressure on the spinal cord, midbrain, and eventually result in central herniation. If the base parts of the brain herniated, it may be irreversible. Some cases of metabolic disorders, poisoning and convulsions may mimic early signs of brain herniation (11).

9. Prognosis of Patients

Loss of consciousness lasting more than 2-4 weeks results in vegetative life. Staying in this position for more than three months for non-traumatic, and more than one year for traumatic patients, will be irreversible (39, 40). Prognosis depends principally on its causes. Mortality after various causes have been reported such as 84% after drowning, 60% after infections, 27% after metabolic disorders, and 2-3% following intoxication (39,40).

Duration of coma and age of patients are important prognostic factors, too. Children younger than 2 years old have a very poor prognosis (30). Lack of response to painful stimuli for 3 days indicate poor prognosis with sensitivity of 70-100% (41). Serial EEG monitoring and evoked potential especially somatosensory one are helpful in prognosis determination.

Furtheremore, regular frequent assessment of respiratory pattern, vital signs, extraocular movement, DTR and body posture is mandatory in all patients with a decreased level of consciousness (*Figure 1*).

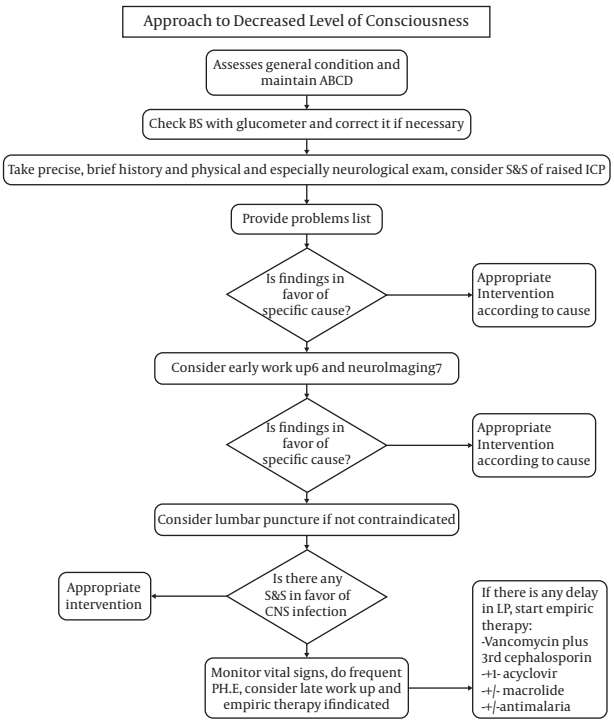

Figure 1. Algorithm for an approach to Child With Decreased Level of Consciousness.

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