Case Report

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A 25-Year-Old Woman with Continues Unconsciousness For 10 Days: A Case Report and Review of Literature

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ABSTRACT

We reported the case of a 25-year-old woman with antihistamine abuse who presented to our hospital with a GCS of 7 and no significant past medical, psychological, or allergic history. We couldn't find any evidence of head trauma, seizures, suicide, or any other metabolic, infectious, intoxication, or electrolyte disturbances. During her 10-day admission, the patient developed non-specific manifestations such as fever, hyperthermia, agitation, hypotension, and sinus tachycardia. Physicians should always consider over-the-counter medicines such as antihistamines as a differential diagnosis for loss of consciousness in patients who do not have any footprints of intoxication in primary urine or blood tests.

Introduction

Consciousness refers to the state in which a person is awake and aware. The depth of wakefulness can be measured by the Glasgow Coma Scale (GCS). Awareness is the ability to respond appropriately to internal and external stimuli [1, 2]. The state of consciousness is divided into coma (a pathologic state without wakefulness or awareness), vegetative state (unresponsive wakefulness syndrome), and minimally conscious state [1, 3].

There is a broad spectrum of disorders that can cause stupor and coma. They are divided into two main groups: structural and functional pathologies. Structural etiologies include trauma and cerebrovascular disease. Nonstructural etiologies are intoxications, infections, seizures, and metabolic derangements [4]. Some of these differential diagnoses are emergencies, such as acute stroke, expanding mass lesion, and herniation syndrome, especially when there is papilledema or focal neurologic deficits in physical examinations, and we can exclude them by head CT scan. Another emergency condition is bacterial meningitis and viral encephalitis presenting with fever. Thus, febrile unconsciousness suggests LP and further CSF evaluation [5]. As mentioned above, metabolic derangements (such as hypoxia, hypoglycemia, hypernatremia, diabetic ketoacidosis, uremia, and hypothyroidism), toxins (including

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lead, cyanide, methanol, and carbon monoxide), and drugs (such as sedatives, barbiturates, opiates, alcohol, anticholinergics, H1-antihistamines, and amphetamines) could also result in a decreased level of consciousness [6, 7].

An important cause of decreased level of consciousness is drug intoxication, unintentional or deliberate poisoning. Deliberate self-poisoning is the most common method of suicide that leads to death or substantial consequences like cardiac, brain, pulmonary, renal injury, and other organ dysfunctions [8-10].

Herein, we report a 25-year-old woman who presented with steady unconsciousness (GCS=7) for 10 days.

Case Presentation

A 25-year-old woman without any past medical history presented to the emergency room of our hospital with an altered level of consciousness. The young woman didn't have any verbal or eye response, even to pain, and in motor response, she localized the painful stimulation (Glasgow Coma Scale (GCS) was 7/15).

According to her family, she was found unconscious lying on the floor with a little foaming at the mouth. Two hours before, her husband confirmed that the patient didn't have any relevant problems. No evidence of suicide was detected. Additionally, she didn't have any history of psychiatric disorders or allergic reactions. Her social history was negative for any drugs or smoking cigarettes. There was no history of seizures, fever, head trauma, or any other medical disorders. Furthermore, no similar history of unconsciousness was reported for her or her entire family.

Her vital signs at the time of admission were as follows: blood pressure (BP): 113/66 mmHg, pulse rate (PR): 88 beats/minute, respiratory rate (RR): 17/minute, temperature (T): 36.6°C, O2 saturation at room air: 97%. In physical examinations, pupils were normal-sized and slightly reactive to light. The plantar reflex and doll's eyes test were negative, as well as nuchal rigidity (negative Brudzinski sign).

She had been intubated immediately in the emergency room because of a decreased level of consciousness. Bedside glucose assessment was 148 mg/dL. Moreover, initial laboratory data didn't show any abnormalities; there wasn't any metabolic disorder to explain the reason for the reduced level of consciousness, infection, or poisoning. An ECG was performed and indicated normal sinus rhythm (Heart rate: 65), normal axis, and no ST-T changes (Figure 1). Echocardiography was done, and left ventricle ejection fraction (EF) was 55-60%, with mild MR and mild TR reported. There wasn't any abnormality. Chest X-ray didn't show any abnormalities. After ensuring her stability, we performed a brain computed tomography (CT) scan on the first day of admission, which showed

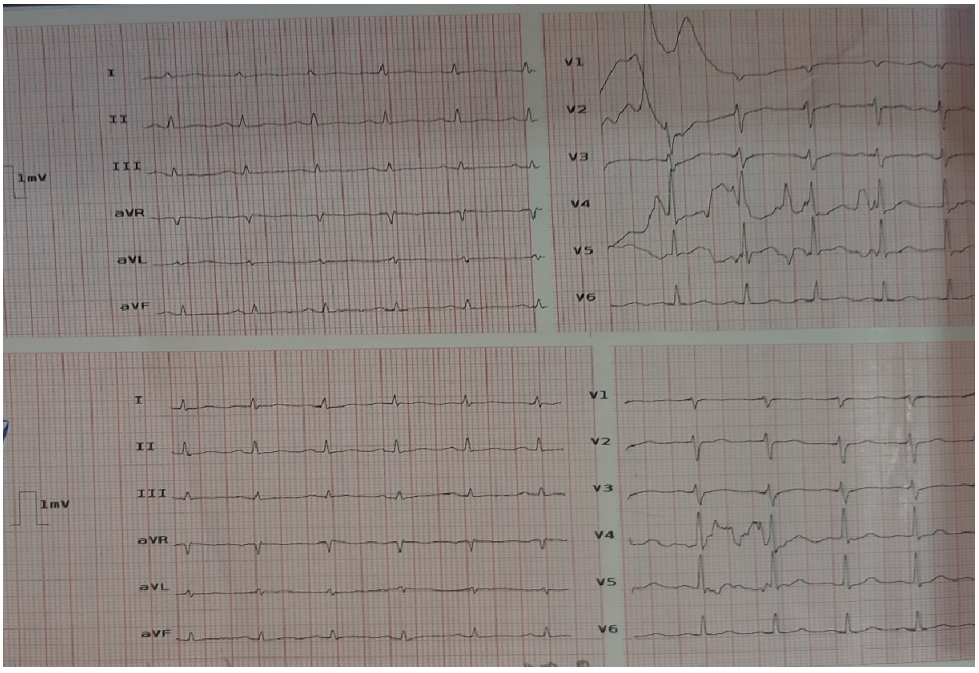

Fig. 1. *ECG of the patient*

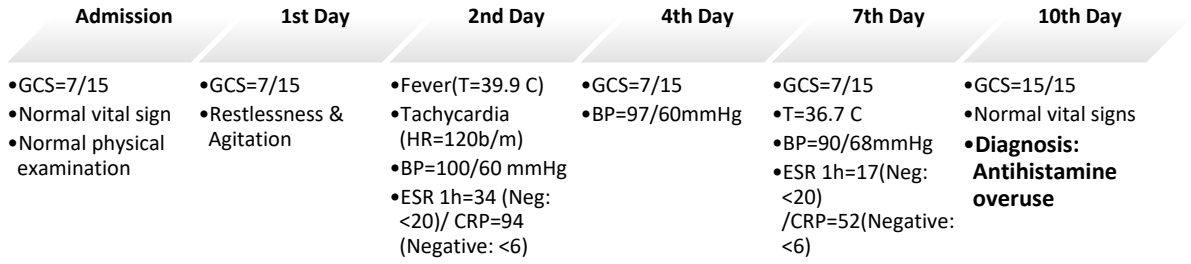

Fig. 2. Time line, GCS: Glasgow Coma Scale, T: Temperature, BP: Blood pressure, HR: Heart Rate, ESR: Erythrocyte sedimentation Rate, CRP: C-Reactive Protein

no signs of acute pathology.

On the next day, the patient's consciousness remained unchanged (GCS=7), and she was admitted to the intensive care unit (ICU). We started sedative medications to control her restlessness, thrashing, and agitation.

On the second day in the ICU, the patient's GCS remained 7, and her vital signs were: PR=120 b/min, BP=100/60. In addition to tachycardia, she unexpectedly developed a fever (T: 39.9°C). A sepsis workup, including urine analysis/culture and blood culture, was done, but both were negative for any source of infection. The patient also developed seizure-like movements, which led to a repeat brain CT, which again showed normal findings. Exploring the source of infection, lumbar puncture (LP) and chest CT scan were reported normal as well. Empiric antibiotic therapy was started in case of any infection. The lab data on the third day were normal for all electrolytes and metabolites except ESR (erythrocyte sedimentation rate) 1h: 34 mm/h (normal: <20), CRP (C-reactive protein): 94.5 (normal: <6), and CPK (Creatine phosphokinase): 4635 (normal: 24-170) (Table 1).

On the 4th day of admission, the patient was still comatose (GCS=7) and became agitated as we reduced sedative agents. She remained febrile and tachycardic. Notably, the patient's blood pressure dropped to 84/37 mmHg with a heart rate of 120 beats/min. Possible reasons could be complications of sedative agents, myocarditis, and endocarditis. We performed an echocardiography, which was normal. We checked serum levels of benzodiazepine, methanol, ethanol, phenytoin, acetaminophen, tricyclic antidepressants (TCA), and salicylate, all of which were undetectable. We did not send any samples for antihistamine plasma or urine levels, as that information was not available in our center.

On the 5th day of ICU admission, the patient remained febrile and unconscious (GCS=7), accompanied by agitation while reducing sedatives. According to her clinical presentation, unchanged level of consciousness, and increased levels of ESR and CRP, we suspected herpes encephalitis, but the HSV PCR test was negative. On the 6th day, the patient remained febrile with a GCS of 7. Regarding serotonin syndrome, although there was no typical presentation such as myoclonus, hyperreflexia, diaphoresis, and shivering, we decided to start cyproheptadine; however, there wasn't any change in the patient's condition.

On the 7th day, her level of consciousness remained the same. Nevertheless, her body temperature and serum levels of ESR and CRP were reduced. Although her condition stayed similar during the 8th and 9th days, on the 10th day, her consciousness surprisingly improved, and within 12 hours, her GCS increased to 15(Figure2).

Laboratory data were absolutely normal at that point. The next day, she was extubated, and the puzzle was solved. She stated that she had taken about 100 pills of antihistamines, not knowing the exact brand name. We performed an EEG (electroencephalogram), which indicated normal waves without any considerable pathology.

Discussion

A 25-year-old woman presented to our hospital with an altered level of consciousness, with no history of psychological disorders or any signs of drug intoxication at the scene. The patient was unarousable and had impaired responsiveness to external stimuli for 10 days. According to the definition of coma (unarousable unresponsiveness), we approached this patient as a comatose patient without a definite reason.

A low level of consciousness can be a life-threatening situation [11]. Therefore, the first line of management for these patients is stabilizing the vital signs and airway assessment [12]. The first intervention in patients with GCS < 8 or in unresponsive patients

Table 1. Serial laboratory results

Test, Unit	Result							Reference Range
Blood biochemistry								
	Admission	1st Day	2nd Day	3rd Day	4th Day	5th Day	Discharge	
BS (blood sugar), mg/dL	148							70-120
AST (aspartate aminotransferase), U/L	22							Up to 35
ALT (alanine transaminase), U/L	11							Up to 45
ALP (alkaline phosphatase), U/L	68							98-279
LDH, U/L	327					497		225-500
C-Reactive Protein		3.3				18	9	negative: <6, Equivocal: 6-9, positive: >9
Creatinine, mg/dL	0.9	0.8						0.6-1.2
Urea, mg/dL	19	11						10-50
Na, mmol/L	138	129	135	135				135-148
K, mmol/L	3.8	5.9	3.4	3.5				3.5-5.3
Ca, mg/dL						8	9.1	8.8-10.2
P, mg/dL	3.6						3.2	2.5-5
Mg, mmol/l	2.4				2.0			1.9-2.5
Alb, g/dl	4.7				3.0			3.6-4.8
CPK Total, U/L			4635			543	121	24-170
Hematology								
WBC, µL	8600	8900						4000-11000
RBC, 10^6/µL	4.03	4.36						4.2-6.3
Hb, g/dL	12.8	13.1						12-16
Hematocrit, %	34.5	35.9						30-45
MCV, fL	85.6	82.3						80-100
MCH, pg	31.8	30.0						27-32
MCHC, g/dL	37.1	36.5						33-38
Platelet, µL	176000	197000						150000-450000
Neutrophil, %	82							--
Lymphocyte, %	15							--
Serology and Endocrinology								
ESR 1h	13	34						<20
COVID-19 RT-PCR	negative							
Benzodiazepine	negative							
Methanol	negative							
Ethanol, mg/dL	negative							600-1800
Phenytoin, µg/ml	<2.5							Toxic level>30
Acetaminophen, ug/mL	0.1							Toxic level:up to 150
Amitriptyline, ug/mL	negative							90-180
salicylate	<0.1							Therapeutic level:20-300 Panic level>500
Urine culture		negative						
Blood Culture		negative						
Gasometry								
pH	7.28	7.39	7.38			7.43		
PCO2	59.7	34.1	41.1			36.8		mm Hg
PO2	165.1	26.6	42.4			48.6		mm Hg
HCO3	26.9	20.6	24.0			24.6		mmol/L
BE		-3.6	-1.0			0.5		mm Hg

to pain is intubation, ventilation, and stabilizing breathing to prevent hypoxemia and brain damage. In circulation assessment, it is important to check pulses and the temperature of extremities to determine if the patient is in shock [6, 13]. In disability evaluation, natural posture, pupil size and reaction, and neck stiffness are important to approximately exclude most emergency situations such as significant neurological injury, intracranial hemorrhage, and meningitis.

Another important reason that should be excluded is hypoglycemia by bedside glucose check [5, 12, 14]. Afterwards, the patient should be examined for any signs of trauma (especially head trauma) or unusual bruising that suggests non-accidental injury [15]. Neurological examinations should be performed to find any brain or brainstem injury. The patient's temperature could also be helpful for diagnosis. Hypothermia appears as a consequence of shock (hypovolemic, hemorrhagic, cardiac, or neurogenic). On the other hand, infections and some medication abuse, including anticholinergic substances, may lead to hyperthermia. Cardiac monitoring and a 12-lead ECG should be taken to exclude arrhythmias. Helpful laboratory exams include blood tests, electrolytes, and biochemistry (sodium, calcium, phosphorus, magnesium, chlorine, glucose), and renal and hepatic function tests to exclude myxedema coma and Addison crisis. Additionally, thyroid function tests and plasma cortisol levels should be evaluated [13, 15].

When we suspect the presence of intracranial lesions, it is necessary to request a head CT scan to assess bleeding (such as subarachnoid hemorrhage, epidural hematoma), tumors, and extensive brain infarcts. If imaging doesn't show any acute pathologic findings, a lumbar puncture should be performed, especially to exclude meningitis or other infections in febrile patients. CSF analysis can also indicate subarachnoid hemorrhage [5, 13, 16].

When there is no evidence to support anatomical or metabolic disorders, drug poisoning becomes more suspected. Approximately 30% of all patients presenting to the emergency department with coma of unknown origin are intoxicated. Toxidromes are helpful to recognize the associated drug. For instance, intoxicated patients with anticholinergic agents present with tachycardia, dry mucous membranes, altered mental status, urinary retention, and hypoactive bowel sounds [12, 17, 18]. As Noyan and his colleagues reported, a 53-year-old man with amitriptyline intoxication demonstrated confusion, tremor, tachycardia, urinary retention, and decreased bowel sounds. Similar to this case, our patient had an altered level of consciousness, tachycardia, and hyperthermia (T=39.9) during her admission course. We didn't have access to all anticholinergic drug tests in our laboratory, but all that we could check, such as TCAs, were negative [19].

Cholinergic drugs cause diarrhea, diaphoresis, miosis, bradycardia, and bronchospasm. Sympathomimetic drugs can induce agitation, mydriasis, tachycardia, hypertension, and hyperthermia [12, 17, 18].

Even therapeutic doses of some medications may cause complications such as an altered level of consciousness in some patients. As Abdi and KaramiZadeh reported, a 76-year-old woman experienced a sudden decreased level of consciousness after taking a therapeutic dose (75 mg) of baclofen for her muscle spasm [20].

On the other hand, some drugs may induce non-specific signs and symptoms, such as antihistamines. Histamines play an important role in the central nervous system (CNS) and affect arousal, cognition, memory, sleep, appetite, emotion, etc. Generally, the term "antihistamines" refers to H1-histamine receptor antagonists, which are the most common cause of antihistamine poisoning among other receptor antagonists. They are used to treat allergic disorders and are widely available, making them a common cause of overdose. Notably, antihistamines can pass the blood-brain barrier and cause both central and peripheral symptoms [21, 22]. Sedating antihistamines often cause anticholinergic effects such as tachycardia, blood pressure disturbance, ataxia, agitation (due to altered CNS regulation), psychosis, etc. Another symptom may be hyperthermia (due to the inability to sweat and impaired CNS thermoregulation). Antihistamines also block alpha 1-adrenergic and serotonin receptors. The main part of the clinical presentation of antihistamine overdose is sedation. Antihistamines block sodium channels, which may lead to arrhythmia like sinus tachycardia and QRS prolongation. Some rare presentations of antihistamines have been reported, such as prolonged coma, rhabdomyolysis, and neuroleptic malignant syndrome [12, 23-25].

Jeffery and his colleagues reported a case of a 26-year-old woman who was intoxicated with 2 full bottles of diphenhydramine. The poison control center recommended starting physostigmine for the patient, but it was a big challenge for us to start antidotes to reverse symptoms because our patient didn't have any psychiatric history, no evidence of committing suicide was detected, and we couldn't measure antihistamine levels in plasma [24].

In another study, a 6-year-old male presented with unintentional cetirizine overdose. Similar to our patient, he was agitated, tachycardic, and febrile. But in contrast to our case, the source of poisoning was obvious, and they could start physostigmine for him to resolve the symptoms [26].

Conclusion

Currently, we approached a case of unconsciousness

in a young woman due to antihistamine overuse. There was no further clue to determine the cause of unconsciousness in this patient. We were forced to monitor the patient and perform a conservative approach as all the assessments reported negative for any potential abnormalities. Surprisingly, after 10 days, she gradually regained consciousness, confessed to antihistamine overuse, and all her symptoms disappeared. This case highlights the necessity of considering over-the-counter medicine overuse in such cases.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this article.

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Conflict of Interests

The authors have no conflict of interest to declare.

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