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A teenager who presented with acute delirium

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A 14-year-old female was brought to emergency department for acute confusion. She was initially conversing normally with friends at a shopping mall, but she was subsequently noted to develop confusion and drowsiness within 15 minutes. There was a transient loss of consciousness without seizure or convulsion, lasting less than one minute, with no reported head injury aside from minor contusions on her limbs. She denied the use of alcohol or substance abuse during the encounter. She had a history of dysthymia and borderline personality traits with follow-up in the psychiatric outpatient department. Her usual medications included promethazine 10mg nocte, lorazepam 0.5mg daily, quetiapine 150mg nocte, and escitalopram 10mg daily.

Upon examination, the patient exhibited a depressed sensorium, with a Glasgow Coma Scale (GCS) of 7/15 (E2, V1, M4). Her pupils are equal, reactive with sizes of 3mm in diameter. There was no scalp wound or hematoma. Vital signs revealed blood pressure of 129/94 mmHg and heart rate of 167 beats per minute. Oxygen saturation was 100% on room air. Her body temperature was normal. The patient was noted to have dry oral mucosa, dry and flushed skin. Neurological assessment indicated hyperreflexia in the knee jerk and plantar reflex, along with mild ankle clonus. Abdominal examination revealed a distended bladder and sluggish bowel sounds.

The electrocardiogram showed sinus tachycardia at a rate of 138 beats per minute, QRS interval of 74ms, and QTc interval of 361ms (Figure 1). Point-of-care blood glucose testing indicated a level of 6.4 mmol/L. Venous blood gas analysis revealed pH of 7.31, pCO2 of 6.5 kPa, pO2 of 5.5 kPa, HCO3 of 24 mmol/L, and base excess of -2.5 mmol/L. The chest X-ray examination was unremarkable.

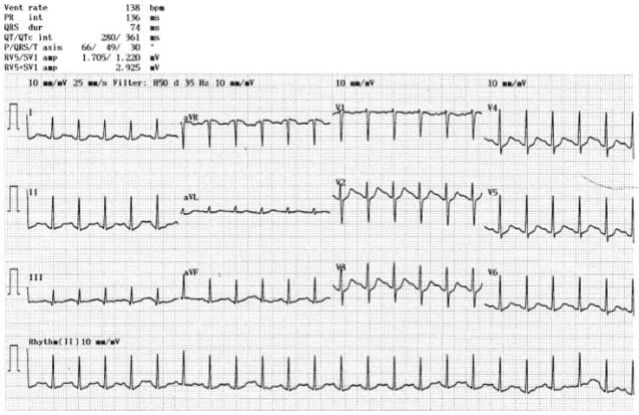

Fig.1 Electrocardiogram of the patient

Meanwhile, a bag containing unlabeled dark blue tablets was discovered in the patient's handbag (Figure 2).


Fig.2 Drug tablets discovered in patient's bag

Differential diagnoses of acute confusion in the young patient

To effectively evaluate acute confusion in an adolescent patient, a thorough history taking is essential. Key components should include:

Onset and Duration of Symptoms:
Details regarding the onset and duration of the symptoms are crucial for establishing a timeline and understanding the progression of the condition.
Medical and Psychiatric History:
A comprehensive review of past medical and psychiatric illnesses is necessary. This should encompass any previous diagnoses, treatments, and hospitalizations.
Medication and Substance Use History:
Detailed information of the patient's medication history, including the use of antidepressants, antipsychotics, and antihistamines, as well as any substance abuse.
Collateral Information:
Information from guardians, family physicians, and the patient's medical records e.g. electronic patient records (ePR) should be obtained to enrich the understanding of the patient's health history and current presentation.

The differential diagnoses of acute confusion in adolescents are extensive and are outlined in Table 1.

Physical examination is essential to rule in or rule out some causes like head injury or sepsis. Clinicians should actively look for toxidromes, including:

- Anticholinergic toxidrome (e.g., confusion, dry flushed skin, hyperthermia, tachycardia, mydriasis, urinary retention, decreased bowel sounds, and myoclonic jerks) (Table 2)
- Sympathomimetic toxidrome (e.g., agitation, diaphoresis, hyperthermia, tachycardia, mydriasis, seizures)
- Sedative toxidrome (e.g., CNS and respiratory depression, miosis, depressed reflexes, relatively stable vital signs)
- Serotonergic toxidrome (e.g., confusion, mydriasis, tremor, tachycardia, diaphoresis, increased reflexes and clonus, diarrhea)

Table 1. Differential diagnoses of acute confusion in an adolescent patient

Category	Potential Causes
Toxicological	- Antidepressants (e.g., TCA, SSRI, SNRI) - Anticholinergics drugs or plants (e.g., promethazine, chlorpheniramine, benztropine, trihexyphenidyl, Datura) - Stimulants (e.g., amphetamines) - Hallucinogens (e.g., LSD) - Etomidate - Opioids - Alcohol intoxication or withdrawal
Metabolic	- Electrolyte imbalance (e.g., hyponatremia, hypocalcemia) - Hypoglycemia - Endocrine crisis, e.g. thyroid storm - Dehydration - Hypoxia
Neurological	- Seizures (particularly in a postictal state) - Intracranial hemorrhage or lesions - Traumatic brain injury
Infectious	- Meningitis, Encephalitis, Sepsis
Psychiatric	- Exacerbation of underlying mental conditions

Table 2. Clinical features of anticholinergic toxidrome

System	Clinical features
CNS	Confusion, agitation, seizure
Eye	Mydriasis & loss of accommodation
CVS	Sinus tachycardia, hypertension
Abdomen	Decreased bowel sounds, urinary retention
Skin	Flushing, dry skin & mucosa
Others	Myoclonic jerking, tremulousness, hyperthermia

Clinical progress of the patient

The clinical presentation was consistent with anticholinergic delirium. Due to uncontrolled agitation, physical restraints were applied. The pediatric on-call team and the Hong Kong Poison Information Centre (HKPIC) doctors were consulted. Titrated doses of physostigmine were administered intravenously under close monitoring, totaling 1 mg (0.1 mg → 0.1 mg → 0.1 mg → 0.2mg, given twice) in the emergency department. The sensorium returned to normal, and agitation resolved 3 minutes upon delivery of a total of 1 mg of physostigmine. The patient was then able to provide further history, admitting that she overdosed 20 to 30 tablets of a blue-colored "allergy medicine." She denied taking any other medications or alcohol. The "allergy medicine" was purchased over the counter at a local pharmacy. However, she could not recall when or where the medication was taken.

Baseline blood tests, including complete blood count, liver and renal function tests, serum calcium, phosphate, and spot glucose, were all normal. Serum paracetamol, salicylate, and ethanol levels were undetectable. The plain CT brain scan was unremarkable.

The patient was admitted to the pediatric intensive care unit (PICU) for close monitoring. Two hours after admission, she developed transient delirium, which was self-limiting, and she did not require further administration of physostigmine or other sedative medications. Five hours after admission to the PICU, cardiac monitoring showed a prolonged QTc interval (499ms). Magnesium sulphate (MgSO4 50% 1.9 mL in 10 mL normal saline) was administered intravenously over 30 minutes. The unknown blue medication was submitted to the in-house pharmacy for identification, with a high likelihood of promethazine 25mg (Phenergan). The medication was not sent to the laboratory for chemical confirmation.

The patient remained clinically stable, with gradual improvement in sensorium. A repeated electrocardiogram on Day 2 showed normal sinus rhythm at a rate of 84/min and a QTc of 437ms. She was transferred to the pediatric general ward two days later. Comprehensive psychiatric assessment was performed after the patient was transferred to general ward to evaluate the reasons for drug overdose and counselling to prevent further episodes of self-harm was provided. She remained stable in the ward was discharged home on Day 7.

Urine drug screening test utilizing Liquid Chromatography Mass Spectrometry identified the presence of promethazine, quetiapine, escitalopram, and citalopram. Considering the patient's drug history, clinical presentation, and rapid response to the cholinesterase inhibitor, physostigmine, the clinical findings are compatible with anticholinergic poisoning resulting from a promethazine overdose.

Discussion

Pediatric delirium and anticholinergic syndrome

Delirium is an acute, fluctuating changes in metal status characterized by disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).[1] Pediatric delirium is not commonly encountered in emergency departments but occurs in as many as 25% of critically ill children in pediatric intensive care units.[2]

The pathophysiology of delirium is complex, involving an interplay of various neurobiological, psychological, and environmental factors. Neuro-biological triggers such as cerebral hypoxia, infection, or inflammation can lead to neuro-inflammation, while metabolic disturbances like dysglycemia, electrolyte imbalances and drug misuse, may affect neurotransmitters such as acetylcholine, dopamine, and serotonin.

Anticholinergic syndrome is one of the causes for delirium. It results from competitive antagonism of acetylcholine at central and peripheral muscarinic receptors. It can occur following the

deliberate ingestion of anticholinergic agents found in some of the common cold medications (e.g., diphenhydramine, chlorpheniramine, promethazine) and certain antidepressants (e.g., tricyclic antidepressants).

Central inhibition leads to agitated delirium, typically manifesting as confusion, restlessness, and hallucinations. Peripheral inhibition may present with hot, dry skin, flushed appearance, mydriasis, tachycardia, decreased bowel sounds, and urinary retention.[4] Typical anticholinergic toxidromes was shown in Table 2. The severity of toxicity can range from mild symptoms to life-threatening conditions, such as seizures and cardiovascular collapse, which may not be solely mediated by muscarinic effects; rather, the drug's effects on other receptors and ion channels are also involved. Polypharmacy overdoses may obscure the classic presentation of the anticholinergic toxidrome.

Promethazine, a first-generation antihistamine, is known for its calming and sedating effects. When combined with other substances like opioids or hallucinogens, these effects can be intensified, potentially leading to hallucinogenic experiences. This heightened effect raises concerns about its potential for abuse.[5] Caution is advised when prescribing or using this medication, especially in patients with a history of substance use disorders.

Management of anticholinergic poisoning

The treatment of delirium involves identifying and addressing its underlying cause after initial stabilization. General measures include supportive care, decontamination, and enhanced elimination. Once the diagnosis of anticholinergic syndrome is suspected, the use of specific antidotes, such as physostigmine, is indicated in selected cases.

Cardiotoxicity

Sinus tachycardia is commonly observed in anticholinergic toxicity.[7] In this case, the patient's heart rate reached 160/min and ECG confirmed sinus tachycardia. This condition is usually self-limiting, and specific treatment to slow the heart rate is rarely necessary. Drug-induced prolonged QRS intervals and associated wide complex tachyarrhythmias can be treated with concentrated sodium bicarbonate.
Prolonged QT intervals can be managed with conventional methods, including close cardiac monitoring, correcting electrolyte disturbances and administering magnesium sulphate infusion.

Central nervous system (CNS) toxicity

CNS toxicity, including agitation and seizures, may occur in severe cases of anticholinergic poisoning. Seizures should be treated with benzodiazepines. It is generally safe to use benzodiazepines for a patient with agitation, especially if the physician is unsure of the poisoning history or is unfamiliar with the use of physostigmine.

Hyperthermia and rhabdomyolysis

Prolonged and uncontrolled agitation may result in hyperthermia and rhabdomyolysis, which can be exacerbated in cases of anticholinergic poisoning. Standard treatments, such as cooling and rehydration, are essential.

Using physostigmine in severe toxicity

Most patients with anticholinergic toxicity respond well to supportive care, but some may benefit from physostigmine.[7,8] This reversible cholinesterase inhibitor can cross the blood-brain barrier and is useful in reversing central anticholinergic poisoning, thereby reducing the need for intubation, ICU admission, sedation, and other invasive procedures such as lumbar puncture. The use of physostigmine in treating anticholinergic toxicity has been reported to be more effective than benzodiazepines.[3] Physostigmine counteracts the anticholinergic effects directly by increasing acetylcholine levels, while benzodiazepines only sedate the confused patient.

Absolute contraindications for physostigmine include:

1. Tricyclic antidepressant (TCA) poisoning[9]
2. New-onset QRS prolongation

The reason why new-onset QRS prolongation is a contraindication is that it suggests sodium channel blockage. Physostigmine can exacerbate cardiotoxicity by increasing vagal tone, potentially worsening bradycardia, AV block or asystole.

While the administration of physostigmine is beneficial in anticholinergic poisoning, caution is essential. If a patient is not experiencing anticholinergic toxicity or if physostigmine is given in excessive amounts, there is a risk of cholinergic toxicity. The symptoms of cholinergic toxidrome may include emesis, bronchorrhea, bronchospasm, lacrimation, sweating, bradycardia, and seizures.

It is recommended that physostigmine be administered by an experienced physician or clinical toxicologist, with cardiac monitoring in place, atropine and other resuscitative equipment readily available as a standby.

For Adult, a typical initial dose of physostigmine is 0.5mg, administered intravenously over 5 minutes, with close observation for clinical response and any signs of cholinergic symptoms. If no response is noted, additional doses of 1-2 mg can be given over 10 minutes. For children, the initial dose 0.02mg/kg (maximum 0.5mg) slow intravenously. In cases where the patient responds positively, there is often a noticeable improvement, including regained consciousness, coherent speech, and reduced tachycardia, as demonstrated in our case. The onset of action of physostigmine occurs within 3-8 minutes, and its duration lasts approximately 1 hour.[9] Repeated doses may be needed in patients with recurrent symptoms.[10]

The most common adverse effects of physostigmine included hypersalivation (9%), followed by vomiting (4.2%), which are self-limiting and treated successfully without complications, while symptomatic bradycardia is a rare complication (0.35%) which can be managed with atropine.[9] Cardiac monitoring and standby IV atropine are therefore recommended when physostigmine is given. Nevertheless, based on evidence from observational studies and case reports, the use of physostigmine appears to be safe, effective, and associated with few complications when administered appropriately.[3,5]

Lessons learned from the case:

- Recognize the differential diagnoses of delirium in the pediatric population. Awareness of toxidromes is crucial in guiding subsequent management.
- Detailed history-taking from parents, guardians, teachers, peers & family doctor, information from patient's medical records combined with relevant circumstantial evidence, is essential for expediting the clinical diagnosis.
- Patients may not present with every feature of the anticholinergic toxidrome, indicating that anticholinergic toxicity should not be ruled out solely based on the absence of one or two features. Pupil may not be very dilated as in our case.
- Pharmacological treatment for anticholinergic toxicity includes benzodiazepines and physostigmine.
- In appropriately selected cases with compatible history, clinical findings, and absence of contraindication, physostigmine is considered safe and effective, helping to avoid unnecessary investigations and treatments.
- Close monitoring for adverse reactions, such as cholinergic crises, along with the availability of atropine and quick access to resuscitation facility, is essential prior to administering physostigmine.

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