Case Report

A girl with a delirium due to an unexpected culprit: a case report

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Abstract

Case presentation: This case describes a girl who presented with severe confusion and agitation, later found to be caused by a diphenhydramine intoxication.
Discussion: Diphenhydramine is an H1-receptor antagonist commonly used as an anti-allergic drug; however, an overdose can result in severe anticholinergic and neurological symptoms.
Conclusion: The differential diagnosis of delirium in a child includes a broad range of aetiologies. Antihistamines are usually considered safe and are readily available, however, diphenhydramine's possible serious side effects warrant careful use.

Introduction: what is unique about this case

A delirium is defined as a sudden central nervous system (CNS) dysfunction, impairing behaviour, cognition and awareness in a previously healthy child (1-3). This can be triggered by a wide range of causes and should be considered as a medical emergency because of the potential severe nature of the underlying pathological processes (2). This case describes a girl who presented with severe confusion and agitation, later found to be triggered by a diphenhydramine intoxication. Diphenhydramine is a H_1-receptor antagonist that can be used as anti-allergic medication, however, an overdose can result in severe neurological symptoms and even death (4).

Case presentation

An 11-year-old girl presented with acute confusion in our emergency department. Her parents explained that she came home earlier that day after buying a snack from a fast-food restaurant. She felt tired and slept for a few hours but did not exhibit any other symptoms at this point. Upon awakening, she was extremely confused and had to vomit. She was disoriented: she could not recall what she did recently or where she was, nor did she recognise her parents. She was shivering and had visual hallucinations.

The girl had no prior medical history and did not take any medication. She was born to consanguineous parents (first cousins), her mother suffers from diabetes and her father has hypertension. There is familial atopy with both her sister and father having mild allergies. Her other three siblings are healthy. Additional history taken regarding possible contact with drugs or medication revealed that losartan, hydrochlorothiazide and metformin were present in the household. She had no contact with any possible drug users.

On physical examination, a markedly confused and agitated girl was seen. She was nonfebrile (36.3°C), hypertensive (153/78 mmHg) and tachycardic (147 beats/min). Heart, lung and abdominal examination were unremarkable. On neurological examination, she was found to have a tremor, an ataxic gait, generalised ataxia and dyspraxia: she grasped aimlessly at her surroundings. Her pupils were normal-sized, equal and reactive to light. Peripheral reflexes were difficult to trigger, Babinski was bilaterally indifferent. No signs of meningeal irritation were seen. The patient was disoriented and was unable to understand and thus complete simple tasks.

Baseline haematological and biochemical investigations were within normal limits (normal blood count, negative CRP, normal electrolytes, glycaemia 78 mg/dL, normal kidney and liver function with slightly elevated LDH of 328 U/L, normal ammonia). Venous blood gas was normal besides a mildly increased lactate of 3.3 mmol/L. Carboxyhaemoglobin was negative. Blood samples for autoimmune encephalitis screening and culture were taken. After initial work-up, intoxication, encephalitis (either infectious or autoimmune) and intracranial space-occupying lesions needed to be excluded as a cause.

The electrocardiogram demonstrated a normal sinus rhythm. Fundoscopy to detect signs of increased intracranial pressure was unremarkable. A computed tomography scan (non-contrast CT-scan) of the brain revealed no signs of intracranial bleeding or space-occupying lesions, encephalitis could not be excluded at this moment. Urine toxicology (standard screening and gamma-hydroxybutyric acid) came back positive for methadone and antidepressants. Although intoxication was the most likely cause, this was an unexpected finding as the family denied the availability of antidepressants or drugs.

Profound agitation and aggression necessitated sedation with propofol, dexmedetomidine, remifentanil and midazolam and she was admitted to our paediatric intensive care unit (PICU) for further monitoring and treatment. An attempt for lumbar puncture failed. Antibiotic and antiviral coverage for CNS infection was considered but not administered since the patient was afebrile and there were no infectious signs in the blood.

Sedatives were gradually weaned over the course of 12 hours. After cessation, a progressive clearance of the neurological symptoms was seen and within a few hours, she was fully recovered. An electro-encephalogram was done after cessation and revealed no signs of epileptic activity. The girl explained that after coming home from the restaurant she had an itchy nose and ingested several tablets of her sister's allergy medication without informing her parents. Her parents did not mention the presence of antihistamines at home since they regarded these as safe. Diphenhydramine is not available for children in Belgium, however, her father purchased it in the United States (US) where it is an over-the-counter anti allergic drug. Additional toxicological testing was positive for diphenhydramine.

The girl was transferred to our paediatric department for further observation, after work-up there were no arguments for further risk of autointoxication and the home environment was considered safe for discharge. An outpatient follow-up one week later revealed a full recovery, there was no indication for additional imaging or follow-up.

Discussion

A delirium or acute confusional state (ACS) refers to a sudden impairment of cognitive function in a previously healthy child (1-3). It should be considered as a medical emergency because of its possible serious underlying pathological processes (2). The overall incidence of ACS in children is unknown, however, it is a relative common presentation in the emergency department (2). A detailed history, physical examination as well as laboratory testing may provide clues for the underlying cause (Table 1) (2, 5). In this case an overdose of diphenhydramine caused acute confusion, however, diagnosis was delayed due to cross reactivity and incomplete history. The causative agent remained unclear until the patient was alert and mentioned taking antihistamines without telling her parents, after which further toxicological testing confirmed the diagnosis.

Table 1 Differential diagnosis acute confusional state in childhood, adapted from M. Prasad, A. Seal and S. R. Mordekar: Fifteen-minute consultation: Approach to the child with an acute confusional state. Arch. Dis. Child. Educ. Pract. Ed. 2017; 102:72-77 (2)

Endocrine	Hypo- and hyperglycaemia Diabetic keto-acidosis Adrenal cortex insufficiency Hypoparathyroidism Hypo- and hyperthyroidism
Infectious	Meningitis, encephalitis, brain abscess Para infectious (Salmonella) Septicaemia
Inflammatory	Autoimmune CNS (Acute Disseminated Encephalomyelitis, anti-NMDA, Hashimoto)
Metabolic	Acidosis/alkalosis Hyponatremia Hyperammonaemia Hepatic encephalopathy Uremic encephalopathy
Neoplastic	CNS neoplasms
Neurological	Postictal state Focal seizures with impairment of consciousness Non-conclusive status epilepticus Basilar migraine, hemiplegic migraine, acute confusional migraine Hydrocephalus
Psychogenic	Conversion Psychosis Delirium
Toxic	Drug abuse/accidents Alcohol Medication side effect Withdrawal Heavy metal intoxication
Traumatic	Post-concussion Intracranial bleeding
Vascular	Arteriovenous malformation-bleed Cerebral vasculitis Hypertensive encephalopathy Hypo- and hypertension, hypovolemia

Diphenhydramine is a frequently used antihistamine, which is available over the counter in several countries. It is a H_1-receptor antagonist that competes with histamine for H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels and respiratory tract (4). Diphenhydramine can bind to central H_1-receptors in the frontal cortex, temporal cortex, hippocampus and pons potentially resulting in significant sedation (4). Peak serum levels are reached two to three hours after oral ingestion. In children, the half-life is five hours on average but ranges between four to seven hours (4). Diphenhydramine is known to produce false positive results in urine detection of methadone and antidepressants due to cross reactivity, which was also seen in our patient (6, 7).

Diphenhydramine is indicated for a wide array of symptoms, including nausea or vomiting, allergic reactions ranging from rhinitis to anaphylaxis, and insomnia (4). In animal studies diphenhydramine was found to stimulate the mesolimbic reward pathway by stimulating dopamine transmission in the nucleus accumbens (8). Unfortunately, these behavioural effects give rise to frequent abuse (4, 8). It is even listed in the top 15 of drugs causing overdose deaths in the US, most of which occur in children age six and younger (4, 9).

Diphenhydramine intoxication can be severe and even fatal due to anticholinergic effects and CNS depression (4, 9). Anticholinergic symptoms are mostly seen in mild to moderate intoxication and include xerostomia, mydriasis, urinary retention, confusion and decreased bowel movements (4, 8, 9). Although used as an anti-emetic drug, high doses can cause vomiting (10). With increasing severity of toxicity additional CNS symptoms are seen, such as severe delirium, seizures, psychosis, dystonia, hallucinations and coma (4, 8, 9). Cardiovascular effects include tachycardia, hypo- and hypertension and cardiac arrhythmias (i.e., QT prolongation and QRS prolongation) (4, 9). Rarely, rhabdomyolysis and renal failure is reported in patients with prolonged agitation, coma, or seizures (4). In this case, our patient presented with tachycardia, hypertension, vomiting, hallucinations, tremor/dystonia, symptoms of delirium (disorientation and agitation) which are all attributable to diphenhydramine (4, 9). Simultaneous use of dexmedetomidine, remifentanil and midazolam with diphenhydramine can worsen the central effects of the latter including delirium, however, these agents were necessary to adequately sedate the patient who was at that point severely agitated and at risk for self-harm (11).

If the patient presents within one hour of ingestion of diphenhydramine, decontamination with activated charcoal may be considered (4). In few cases a trial with the parasympathomimetic alkaloid physostigmine was done to reverse the anticholinergic effects, however, this was only successful in half the cases (9). There is no other antidote known to reverse the effects of diphenhydramine toxicity, so the mainstay of therapy remains supportive (4).

Diphenhydramine is available in Belgium as a sleep aid (Nutasium) and for nausea, vomiting and motion sickness (R Calm) (12). However, its use is not recommended by the Belgian Centre for Pharmacotherapeutic Information (BCFi/CBiP) given the risk of abuse (for recreational purposes) and addiction, especially in adolescents and young adults (12, 13).

The use of antihistamines in paediatrics is indicated for allergy symptoms including rhinitis, asthma, urticaria, atopic dermatitis and acute allergic reactions (14).

The use of second-generation antihistamines for allergy in children is preferred to that of first-generation products due to the low incidence of central side-effects (14,17). In contrast, intoxication with first generation antihistamines (e.g., diphenhydramine) can cause lethargy and anticholinergic like symptoms including flushing, hallucinations, seizures, hypertension and fever (14-17). Severe intoxication can even be fatal due to refractory seizures and cardiopulmonary arrest (14). Second or third generation antihistamines (e.g., cetirizine and desloratadine) have a better safety profile (15,16). A French study concluded that only 9% of children with an overdose of H_2-antihistamines were symptomatic and none exhibited severe symptoms (16).

Conclusion

The differential diagnosis of delirium in a child includes a broad range of aetiologies. Diphenhydramine was found to be the unexpected culprit in this case. Although antihistamines are usually considered safe and are readily available, the serious side effects of diphenhydramine warrant careful use.

The authors have no conflict of interest to declare.

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