A sabbath in the emergency room or a case of anticholinergic toxicity?

Antonio Agosti,[1] Silvia Bricchi,[1] Francesca Rovati,[1] Mara Vancea Opris,[1] Davide Giulio Ponzi,[1] Francesco Mariani,[1] Nicola Morelli,[2] Andrea Magnacavallo,[1] Andrea Vercelli,[1] Erika Poggiali[1]

[1]Emergency Department, Guglielmo da Saliceto Hospital, Piacenza; [2]Neurology Unit, Guglielmo da Saliceto Hospital, Piacenza, Italy

Abstract

We report the case of a 32-year-old Italian man admitted to our emergency room for visual disturbances with blurred vision, anisocoria and temporal headache suddenly occurred in absence of other neurological symptoms. A diagnosis of *Datura stramonium*-induced anticholinergic toxicity was done. With our work, we want to highlight the importance of a meticulous clinical examination, including papillary diameter and reflexes, combined with a detailed history of the patient in the emergency room. Anticholinergic toxicity is a medical emergency. The diagnosis is always clinical, and it can represent a challenge for the emergency clinicians because it can mimic several neurological diseases, including acute stroke and seizures, but early diagnosis is crucial to avoid severe complications and management errors.

Correspondence: Erika Poggiali, Emergency Department, "Guglielmo da Saliceto" Hospital, Via Giuseppe Taverna 49, Piacenza, Italy.
Tel.: +39 0523 303044. E-mail: poggiali.erika@gmail.com

Key words: Anticholinergic toxicity; anticholinergic syndrome; *Datura stramonium*; toxic plants.

Acknowledgements: The authors thank the Poison Control Centre of Pavia for the precious help in the management of all the patients admitted to their emergency department for intoxication.

Contributions: AA and EP drafted the manuscript. SB, FR, MVO, DGP, FM and NM cared for the patient. NM, AM e AV critically revised the manuscript. All authors approved the final version and stated the integrity of the whole work.

Conflicts of interest: The authors declare no conflict of interest. EP is member of the editorial board of Emergency Care Journal.

Availability of data and materials: All data underlying the findings are fully available.

Ethics approval and consent to participate: As this was a descriptive case report and data was collected without patient identifiers, ethics approval was not required under our hospital's Institutional Review Board guidelines.

Informed consent: The patient provided consent for the access to medical records at the time of admission.

Received for publication: 21 November 2021.
Revision received: 3 January 2022.
Accepted for publication: 1 February 2022.

Licensee PAGEPress, Italy
Emergency Care Journal 2022; 18:10292
doi:10.4081/ecj.2022.10292

Highlights

- *Anticholinergic syndrome is a real medical emergency.*
- *Anticholinergic syndrome should always be considered in the differential diagnosis of a sudden onset of altered mental status.*
- *Medications, psychoactive drugs, homeopathic solutions, and toxins can cause anticholinergic syndrome with fatal outcome.*
- *Plant-induced anticholinergic syndrome should be always considered and investigated.*
- *Datura stramonium and Atropa belladonna are the most common cause of anticholinergic toxicity.*

Case description

A healthy 32-year-old Italian man presented to our emergency room due to acute onset of blurred vision and right temporal headache occurring within the previous two hours. He was very agitated. He referred a recreational use of marijuana. Anisocoria was detected with his right pupil dilated (6-7 mm) and not responding to light. His skin was dry and hot. His vital signs on check-in were heart rate 102 bpm, blood pressure 124/85 mmHg, body temperature 37.5°C, respiration rate 20/min, and pulse-oximetry 98 % on room air. Electrocardiogram (EKG) revealed a sinus tachycardia with a rate of 110 bpm. The remaining physical examination was normal. A Computed Tomography (CT) of the brain was performed to exclude acute stroke or other brain damage. Laboratory findings showed increased level of creatinine kinase (490 U/L, normal value 0-172). Full blood count, renal and hepatic function, coagulation time and C-reactive protein were all within the normal range. Urine drug screen resulted negative for drugs of abuse. Ethanol was absent. Intravenous fluids (0.9% saline water solution 1000mL) were administered. Treatment with delorazepam 2 mg IV helped to control the agitation as well as the tachycardia. Repeat dosing was not required, and over the course of six hours his symptoms completely solved. A detailed patient's history revealed that the patient was a gardener who had been handling the plant of *Datura stramonium* all day without protective gloves. *Datura stramonium* is a plant with well-known anticholinergic properties. It was considered as the aetiology of his symptoms as no other causes were identified. Neurological evaluation confirmed the diagnosis of plant-induced anticholinergic toxicity. We consulted the Poison Control Centre of Pavia, that confirmed the diagnosis and the complete reversibility of all the symptoms, including anisocoria, without sequelae. After a 6-hour observation time in the emergency room, the patient was discharged in good clinical condition, completely asymptomatic, with normal pupils.

Discussion

Anticholinergic syndrome results from the inhibition of mus-

carinic cholinergic neurotransmission. It can be due to several causes, including medications, toxins, and some plants. Medications include anticholinergic drugs, antihistamines, tricyclic antidepressants, and parasympatholytic agents (*i.e.*, atropine, scopolamine, and hyoscyamine),[1] and homeopathic solutions due to a production error of the homeopathic dilution.[2] BZ (agent 15), botulism and the ingestion of *Amanita muscaria* mushrooms can cause anticholinergic syndrome.

Plant-induced anticholinergic syndrome

The ingestion of particular plants may induce anticholinergic syndrome, which is caused by their alkaloid metabolites (atropine, scopolamine, and hyoscine) as defence mechanism against insects and predators.[3,4] They include *Solanaceae* family (*Mandragora officinarum*, "Mandrake"; *Mandragora autumnalis*, "Devil's herb"; *Hyosciamus niger* and *H. reticularis*, known as "henbane"; *Burgmansia* spp., "Angel's Trumpet"), *Datura* spp. (*Datura inoxia* "Moonfl ower", *Datura stramonium* "Jimson weed", *Datura metel* "Devil's trumpet"); *Solanum erianthum*, *Garryaceae* family (*Garrya* spp.), *Bignoniaceae* family (Campsis grandiflora), *Papaveraceae* family (*Lamprocapnosspectabilis*, "bleeding heart"),[5] and *Aquifoliaceae* family (*Ilex paraguariensis*, "Herba mate"). The anticholinergic effects are dose-dependent and represent a medical emergency.[3]

Atropa belladonna and *Datura stramonium* belong to *Solanaceae* family and are the most common cause of anticholinergic toxicity. Both of them are present worldwide and well known in the literature for their hallucinogenic effects used for medical and religious purposes.[6-9] Their ingestion can be accidental, particularly in children,[10,11] or by contaminated honey,[12] herbal toothpaste[13] and tea,[14-16] although the most of reported cases in literature occur as a result of deliberate use for their hallucinogenic effects.[17,18]

Atropa belladonna is also known as "deadly nightshade" and it has a long history of use as a pharmaceutical cosmetic. Its foliage and berries are extremely toxic for the high concentration of tropane alkaloids. Berries are black, globular, and sweet, and are consumed by animals that disperse the seeds in their droppings. They can be easily mistaken for blueberries leading to accidental ingestion, causing both anticholinergic syndrome and liver damage.[19-22] Atropine, which is commonly used in clinical practice, is derived from *Atropa belladonna*.

Datura stramonium, also known as "Jimson weed", was used in the past traditional medicine to treat asthma and relief pain. It extremely toxic and can cause coma, because all its parts contain high concentration of tropane alkaloids with an estimated value of 0.20mg atropine and 0.65mg scopolamine per blossom.[17,23]

Here we report the classical clinical presentation with signs and symptoms, the differential diagnosis, and the correct management of anticholinergic toxicity.

Symptoms

The clinician must be familiar with the anticholinergic toxidrome as a reliable history is not always obtainable. The diagnosis is always clinical. Signs and symptoms are caused by central and/or peripheral nervous system effects and can be easily remembered with this mnemonic: "red as a beet, dry as a bone, blind as a bat, mad as a hatter, hot as a hare, and full as a flask". The mnemonic refers to the clinical signs due to peripheral blockage of the parasympathetic postganglionic muscarinic receptors, *i.e.*, flushing, dry skin (particularly in anxilla and groin), eyes and mucous membranes, mydriasis with loss of accommodation (cycloplegia), altered mental status, increased body temperature, and constipation and urinary retention, respectively.

The patient can present an altered level of consciousness characterized by soft spoken speech or mumbling word salad, agitation, restlessness, confusion, hallucinations, delirium, and coma. Sometimes, speech can sound muffled as if cotton balls are in mouth, due to its dryness. Seizures and jerking movements can be possible.[24,25] Anticholinergic toxicity can be confused with sympathomimetic toxicity. However, the absence of sweating indicates anticholinergic toxicity.[24]

A standard approach based on the "ABC" method is recommended for any suspected poisoned patient. Evaluation of the patient's airway, respiratory, and circulatory status are mandatory and should immediately be performed. Vital signs including body temperature, heart rate, respiratory rate, blood pressure, and oxygen saturation should be obtained at admission and continuously monitored. The patient should also be placed on continuous cardiac monitoring and have intravenous access established.

Laboratory findings, EKG, and imaging

Diagnostics including urinalysis, urine drug screen, fingerstick glucose, salicylate and acetaminophen levels and pregnancy test for females should be obtained. Creatinine kinase (CK) levels should be monitored with serial measurements for possible development of rhabdomyolysis. EKG is mandatory. Absolute contraindication for the use of physostigmine are bradycardia, intraventricular conduction delay (wide QRS), AV nodal block, and terminal R (wide R wave > 3 mm) in aVR.[26] A brain CT scan can be used to exclude an alternative diagnosis. In case of fever or seizures, a lumbar puncture can be helpful to exclude a central nervous infection.

Management

If early diagnosed and promptly treated with adequate supportive care, the anticholinergic syndrome has a good prognosis. Agitation always require treatment and can become a challenge in patients with severe anticholinergic syndrome. Benzodiazepines administered intravenously are the drugs of choice.[27] Large doses can be required to avoid fatal complications such as hyperthermia and rhabdomyolysis. Dexmedetomidine[28] and a short course of propofol can be also used in the emergency setting. Physical restraints should be avoided due to the risk of worsening rhabdomyolysis. Antipsychotic, *e.g.*, haloperidol, are contraindicated for the risk of upsetting temperature regulation with worsening hyperthermia.[26] Temperature must be accurately monitored, and adequate intravenous fluids infused, particularly the case of hypotension or if rhabdomyolysis is suspected.[29]

Physostigmine may be indicated in severe cases refractory to benzodiazepines.[30-32] It is a reversible acetylcholinesterase inhibitor that increases acetylcholine concentration in the synaptic cleft, and it is used as antidote in cases of altered level of consciousness and other signs of anticholinergic toxicity.[30-32] Due to its ability to cross the blood brain barrier, physostigmine can reverse both central and peripheral toxicity.[33-35] In unclear cases physostigmine can aid diagnosis: when administered, it can transiently reverse anticholinergic effects. Repeated doses every 30 minutes may be needed. It can be administered using different routes: i) intramuscular: 0.05mg/kg in adults and 0.02 mg/Kg in children; ii) intravenous: 0.02mg/kg up to 1-2mg infuse over 2-10 minutes or slower and repeatable every 30 minutes in patients with persistent altered mental status (as often as every 10-20 min); iii) oral, diluted in juice to reduce bitter taste. The dose of 2-4 mg IV slowly every

2-4 hours prn can be used as maintenance. A rapid infusion can cause seizures. Taper must be done slowly over hours to 4-5 days.[36] A toxicology consult must be required for every patient, especially if more than one dose is needed. In addition, emergency clinicians must always remember that physostigmine is contraindicated in uncontrolled asthma or wheezing, seizure disorders and bowel obstruction.[37] EKG is mandatory before its administration. Common side effects include bradycardia, bronchorrhea, and vomiting. Bradycardia is related to increased vagal tone. Atropine 0.5 to 1 mg may be given to counter significant bradycardia or bronchorrhea. Pre-treatment with ondansetron can be considered to reduce the risk of vomiting.

In case of toxic plant ingestion, gastric lavage and activated charcoal may be useful if the ingestion occurred within one hour before the patient. However, administration somewhat outside this window may be appropriate, as anticholinergics decrease gastrointestinal motility.[38,39]

In patients with severe altered GCS score, intubation should be considered before gastric lavage. In all the other cases, respiratory support is not required. If wide-complex dysrhythmias develop, IV sodium bicarbonate should be administered.[40,41] Bladder catheterization should always be considered as a measure for urinary retention management.

When dealing with a patient with suspected or diagnosed anticholinergic syndrome, emergency clinicians must always keep in mind all the possible complications, that include respiratory failure, cardiovascular collapse, rhabdomyolysis, coma, permanent disability and death. Moreover, specialist consults could be indicated depending on the severity of the symptoms: poison control in all the cases, intensivist for intensive care unit admission, psychiatry in case of intentional self-harm ingestion, and nephrology if dialysis is necessary.

Differential diagnosis

Anticholinergic syndrome can mimic other central nervous system conditions that must be always excluded. Emergency clinicians should consider differential diagnosis such as sympathomimetic toxicity, serotonin syndrome, malignant hyperthermia,[42] neuroleptic malignant syndrome,[43] delirium,[44] encephalitis and sepsis.[45] In addition, psychoactive drugs should be included in the differential diagnosis.

Conclusions

Anticholinergic toxicity/syndrome represents a real medical emergency. The early diagnosis can be difficult because plant-induced anticholinergic toxicity can mimic several diseases, including central nervous system diseases, such as acute stroke and seizures. Physicians should always consider plant intoxication in presence of acute onset of consciousness alteration combined with signs of anticholinergic toxicity and a medical history of vegetal ingestion or prolonged contact, and use of hallucinogenic drugs. When a severe altered state of consciousness is present, physostigmine is the antidote of choice. In our case, there was no need for physostigmine at all, due to the mildly altered mental status and the immediate improvement of the patient's clinical situation after the administration of benzodiazepines and fluids, which are the first-line therapy for agitation. Overall, with early identification and adequate supportive care, the prognosis of anticholinergic toxicity is good as observed in our case.

References

1. Marchlewski MB. Anticholinergic syndrome. Avoiding misdiagnosis. J Psychosoc Nurs Ment Health Serv 1994;32:22-4.
2. Schmoll S, Romanek K, Zorn G, Eiglmeier H, Eyer F. Anticholinergic syndrome after atropine overdose in a supposedly homeopathic solution: a case report. Clin Toxicol (Phila) 2021;14:1-3.
3. Soulaidopoulos S, Sinakos E, Dimopoulou D, et al. Anticholinergic syndrome induced by toxic plants. World J Emerg Med 2017;8:297-301.
4. Jerzykiewicz J. Alkaloids of Solanaceae (nightshade plants). Postepy Biochem 2007;53:280–6.
5. Jeong TO, Lee JB, Jin YH, Yoon JC. Anticholinergic syndrome following ingestion of Lamprocapnos spectabilis (Bleeding Heart). Clin Toxicol (Phila) 2015;53:842-3.
6. Pigatto AGS, Blanco CC, Mentz LA, Soares GLG. Tropane alkaloids and calystegines as chemotaxonomic markers in the Solanaceae. An Acad Bras Cienc 2015;87:2139–49.
7. Chang SS, Wu ML, Deng JF, Lee CC, et al. Poisoning by Datura leaves used as edible wild vegetables. Vet Hum Toxicol 1999;41:242–5.
8. He J, Hou XY. The potential contributions of traditional Chinese medicine to emergency medicine. World J Emerg Med 2013;4:92–7.
9. Gowdy JM. Stramonium intoxication: review of symptomatology in 212 cases. JAMA 1972;221:585–7.
10. Disel NR, Yilma M, Kekec Z, Karanlik M. Poisoned after dinner: Dolma with datura stramonium. Turk J Emerg Med 2016;15:51–5.
11. Rakotomavo F, Andriamasy C, Rasamoelina N, Raveloson N. Datura stramonium intoxication in two children. Pediatr Int 2014;56:e14–6.
12. Ramirez M, Rivera E, Ereu C. Fifteen cases of atropine poisoning after honey ingestion. Vet Hum Toxicol 1999;41:19–20.
13. Pereira CA, Nishioka S de D. Poisoning by the use of Datura leaves in a homemade toothpaste. J Toxicol Clin Toxicol 1994;32:329–31.
14. Acikalin A, Gulen M, Kara B, et al. Anticholinergic syndrome and supraventricular tachycardia caused by lavender tea toxicity. Keio J Med 2012;61:66-8.
15. Diker D, Markovitz D, Rothman M, Sendovski U. Coma as a presenting sign of Datura stramonium seed tea poisoning. Eur J Intern Med 2007;18:336–8.
16. Pekdemir M, Yanturali S, Akay S, et al. Acute anticholinergic syndrome due to Datura innoxia Miller mixed with lime tea leaves. Vet Hum Toxicol 2004;46:176–7.
17. Guharoy SR, Barajas M. Atropine intoxication from the ingestion and smoking of jimson weed (Datura stramonium). Vet Hum Toxicol 1991;33:588–9.
18. Shervette RE, Schydlower M, Fearnow RG, Lampe RM. Jimson "loco" weed abuse in adolescents. Pediatrics 1979;63:520–3.
19. Trabattoni G, Visintini D, Terzano GM, et al. Accidental poisoning with deadly nightshade berries: a case report. Hum Toxicol 1984;3:513–6.
20. Mateo Montoya A, Mavrakanas N, Schutz JS. Acute anticholinergic syndrome from Atropa belladonna mistaken for blueberries. Eur J Ophthalmol 2009;19:170–2.
21. Caksen H, Odabaş D, Akbayram S, et al. Deadly nightshade (Atropa belladonna) intoxication: an analysis of 49 children. Hum Exp Toxicol 2003;22:665–8.

22. Berdai MA, Labib S, Chetouani K, Harandou M. Atropa Belladonna intoxication: A case report. Pan Afr Med J 2012;11:72.
23. Adegoke S, Alo L. Datura stramonium poisoning in children. Niger J Clin Pract 2013;16:116–8.
24. Holstege CP, Borek HA. Toxidromes. Crit Care Clin 2012;28:479-98.
25. Lin TJ, Nelson LS, Tsai JL, et al. Common toxidromes of plant poisonings in Taiwan. Clin Toxicol (Phila) 2009;47:161-8.
26. Dawson AH, Buckley NA. Pharmacological management of anticholinergic delirium - Theory, evidence and practice. Br J Clin Pharmacol 2016;81:516–24.
27. Broderick ED, Metheny H, Crosby B. Anticholinergic Toxicity. 2021 Aug 1. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 30521219.
28. Bross MH, Nash BT Jr, Carlton FB Jr. Heat emergencies. Am Fam Physician 1994;50:389-96.
29. Walker A, Delle Donne A, Douglas E, et al. Novel use of dexmedetomidine for the treatment of anticholinergic toxidrome. J Med Toxicol 2014;10:406-10.
30. Moore PW, Rasimas JJ, Donovan JW. Physostigmine is the antidote for anticholinergic syndrome. J Med Toxicol 2015;11:159-60.
31. Dart RC, Borron SW, Caravati EM, et al. Expert consensus guidelines for stocking of antidotes in hospitals that provide emergency care. Ann Emerg Med 2009;54:386–94 e1.
32. Schneir AB, Offerman SR, Ly BT, et al. Complications of diagnostic physostigmine administration to emergency department patients. Ann Emerg Med 2003;42:14–9.
33. Derinoz O, Emeksiz HC. Use of physostigmine for cyclopentolate overdose in an infant. Pediatrics 2012;130:e703-5.
34. Watkins JW, Schwarz ES, Arroyo-Plasencia AM, Mullins ME. The use of physostigmine by toxicologists in anticholinergic toxicity. J Med Toxicol 2015;11:179–84.
35. Burns MJ, Linden CH, Graudins A, et al. A comparison of physostigmine and benzodiazepines for the treatment of anticholinergic poisoning. Ann Emerg Med 2000;35:374–81.
36. Somani SM, Khalique A. Pharmacokinetics and pharmacodynamics of physostigmine in the rat after intravenous administration. Drug metabolism and disposition: the biological fate of chemicals 1987;15:627–33.
37. Walker WE, Levy RC, Hanenson IB. Physostigmine–its use and abuse. JACEP 1976;5:436–9.
38. Green R, Sitar DS, Tenenbein M. Effect of anticholinergic drugs on the efficacy of activated charcoal. J Toxicol Clin Toxicol 2004;42:267-72.
39. Isbister GK, Kumar VV. Indications for single-dose activated charcoal administration in acute overdose. Curr Opin Crit Care 2011;17:351-7.
40. Sharma AN, Hexdall AH, Chang EK, Nelson LS, Hoffman RS. Diphenhydramine-induced wide complex dysrhythmia responds to treatment with sodium bicarbonate. Am J Emerg Med 2003;21:212-5.
41. Holger JS, Harris CR, Engebretsen KM. Physostigmine, sodium bicarbonate, or hypertonic saline to treat diphenhydramine toxicity. Vet Hum Toxicol 2002;44:1-4.
42. Jamshidi N, Dawson A. The hot patient: acute drug-induced hyperthermia. Aust Prescr 2019;42:24-28.
43. Catterson ML, Martin RL. Anticholinergic toxicity masquerading as neuroleptic malignant syndrome: a case report and review. Ann Clin Psychiatry 1994;6:267-9.
44. Ista E, van Dijk M. We Can Not Compartmentalize Our Patients! Overlapping Symptoms of Iatrogenic Withdrawal Syndrome, Pediatric Delirium, and Anticholinergic Toxidrome. Pediatr Crit Care Med 2017;18:603-604.
45. Agarwal P, Bansal S, Sharma A, Saini VK. Atropine poisoning mimicking septicemia. Ann Neurosci 2014;21:34-5.