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Anticholinergic psychosis: Differential diagnosis and management

ABSTRACT: The central anticholinergic syndrome occurs frequently but is often unrecognized because many patients' symptoms do not appear in a well-defined pattern. Symptoms range from confusion and agitation to coma. Two brief case reports illustrate the presentation and diagnosis of the syndrome. Its management, including psychological support and the administration of physostigmine, is discussed.

The central anticholinergic syndrome (CAS) has become a growing problem in clinical practice. Many over-the-counter compounds, prescription medications, and "street drugs" contain the anticholinergic agents that produce the syndrome. In fact, there are over 600 anticholinergic compounds currently on the market.[1] Although ubiquitous, anticholinergic drugs are often difficult to identify as causative agents in presenting clinical syndromes whose prevalence may not be recognized widely. The practicing clinician often expects the syndrome to appear in a well-defined pattern, but while there are general features of the clinical presentation, many patients may not demonstrate a classic picture. The response to medications varies among patients, and there is a temporal fluctuation in the course of an anticholinergic syndrome.[2]

Clinical presentation

CAS occurs when central and peripheral cholinergic function is decreased.[3] Features of delirium and parasympathetic shutdown are observed. Patients are often confused, agitated, and may experience visual and auditory hallucinations as well as memory impairment (typically, recent memory). In addition, they may evidence dry skin, flushed face, dry mouth, constipation, urinary retention, abdominal distress, tachycardia, and dilated pupils that are poorly reactive to light. Other symptoms include poor motor coordination, ataxia, dysarthria, and increased muscular tone followed by profound muscular weakness and myotonic twitching. Impairments of all kinds may range in degree from mild to severe. With large doses of anticholinergic agents, coma can occur.[2,4]

The group at high risk for developing this syndrome includes children and the elderly. Children typically present with agitation, restlessness, hyperactivity, and the sudden occurrence of violence. Often no clear history of ingesting the medication of a parent or substances such as belladonna plants can be elicited. The presentation in geriatric patients is variable. One symptom is grasping at imaginary objects or picking at bedclothes. The most reliable signs of the central anticholinergic syndrome include dilated and poorly reactive

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pupils, confusion, disorientation, recent memory disturbance, flushed face, dry mucous membranes, visual hallucinations, tachycardia, restlessness, hyperactivity or agitation, ataxia, and decreased motor coordination. These findings may occur in susceptible patients receiving usual doses of psychotropic medications, particularly when sedating phenothiazines and antidepressants are administered concurrently.

In severe cases, somnolence and coma may occur. It should be noted, however, that somnolence and coma develop in less than one third of those patients diagnosed as having central anticholinergic syndrome. Also, coma is twice as likely to develop in an adult as in a child, and generally it occurs late in the course of the syndrome.[2]

Often the geometric potentiation of two anticholinergic drugs is overlooked. Cases of intentional self-intoxication with plant alkaloids, such as angel's trumpet[5] and ginseng weed, have been reported in young adults, who, along with adolescents, are also using phencyclidine (PCP) in increasing numbers. Many of the toxic psychoses secondary to the ingestion of this substance are not due to its anticholinergic action. Nonetheless the drug does have anticholinergic properties, which may contribute to the form and presentation of its effects and to the subsequent development of complications.

Since cognitive function is impaired by anticholinergic agents, the patient often gives an unreliable history. Thus, information from other persons is often crucial to making a correct diagnosis. It is especially important to obtain a complete medication history. Two typical cases follow.

Case 1

A 67-year-old woman was brought to an emergency room from a local nursing home. Reportedly, she had been increasingly withdrawn during the two previous weeks. The diagnosis of depression had been made, and she had been started on one of the tricyclics known to have anticholinergic effects. The depression was not alleviated. Instead, the patient developed a flushed face, dry skin, and a slight fever; and she became confused and agitated. The physician in the emergency room made the diagnosis of CAS secondary to prescribed tricyclic ingestion. The medication was discontinued, and the patient's health returned to normal.

Case 2

A 44-year-old man had a long-standing problem with initial insomnia. He was treating himself by taking an over-the-counter medication that included scopolamine. Not finding this effective, he increased the dosage on his own to two and then three capsules a night, assuming that an over-the-counter preparation must be fairly innocuous. One night, after taking three capsules at bedtime, he awoke in the middle of the night and, upon having difficulty falling asleep again, took a fourth capsule. His wife called paramedics for help an hour later when the patient started screaming that there were people trying to break through the windows and that he had to "get out of here and go back home." When seen in an emergency room, he demonstrated a widened pulse pressure, tachycardia, and dilated pupils poorly responsive to light. He was successfully treated with physostigmine (2 mg administered intramuscularly) and returned to a normal state of health within eight hours.

CAS can develop following a suicide attempt using anticholinergic drugs or after incorrect drug administration to a hospital inpatient. It can also occur in outpatients who medicate themselves. Inappropriate drug ingestion may be especially prevalent in persons with an organic impairment who are taking medication as outpatients. Psychiatrists and other physicians often see CAS in patients who have been receiving neuroleptics, tricyclics, and/or antiparkinsonism agents in combination. Thirteen percent of all patients treated with tricyclic antidepressants and 35% of patients over the age of 40 treated with phenothiazines plus antiparkinsonism drugs have been reported to develop toxic confusional states.[6] Agitated and depressed patients, especially if they are elderly, may present a particular problem. Often such patients will be given an antipsychotic agent and a tricyclic in combination. If the agitation increases or does not resolve, however, the question arises as to whether the medications themselves are causing a problem—CAS or akathisia. If the CAS is overlooked, increasing doses of the causative medications can dangerously worsen the syndrome. One approach is to first administer a neuroleptic to control disruptive behavior and later begin low doses of tricyclics, if needed, to alleviate depressive symptoms.

Management

If a red face and dry mouth seem to indicate CAS, checking for dilated pupils, widened pulse pressure, tachycardia, and hyperthermia is useful in clarifying the diagnosis. If CAS is suspected, a test dose of physostigmine can be administered. Typically, the adult patient receives an intramuscular injection of 1 to 2 mg of physostigmine and is then closely observed for 30 minutes. If the response is dramatic

improvement, the diagnosis is confirmed.[7] The mental status will return to normal, tachycardia will abate, and the dryness of the mouth will subside. Mydriasis, however, may persist for several days if parasympathetic over-stimulation occurs. Since physostigmine has a short half-life—generally under one hour—improvement following each dose is likely to be of brief duration.

Generally, physostigmine remains the treatment of choice for CAS. Clinicians vary in how they use it, however. Some feel that it should be used only in moderately severe cases because of the possible danger of its administration to a comatose patient.[8] Some investigators, however, report that physostigmine can be effective in cases of coma.[9] Usually the drug is administered to the symptomatic patient—without either reserving it for or withholding it from severely affected patients. After taking a physical examination and a history (including questions on allergies, bradycardia, and bronchial constriction), injections can be administered every 30 to 60 minutes, depending on the clinical course of the syndrome. Physostigmine is a tertiary amine, which rapidly crosses the blood-brain barrier and thus alleviates central nervous system effects as well as peripheral anticholinergic blockade.

The drug inhibits anticholinesterase and thereby promotes the action of the primary neurotransmitter, acetylcholine. The effects of physostigmine can be very complex since at any moment multiple actions of acetylcholine can occur in preganglionic, postganglionic, somatic motor, and central nervous system receptors. There is particular intricacy in the parasympathetic activities of the cardiovascular system.[10] Physostigmine has predominantly parasympathetic effects, but by virtue of preganglionic stimulation it can have sympathetic influences as well.[10]

Acute complications following the administration of physostigmine can include precipitation of asthmatic episodes, and heart block resulting in myocardial infarction. Toxicity resulting from physostigmine may be reversed by the administration of 0.5 mg of atropine sulfate for each milligram of physostigmine administered.[11] Relative contraindications to physostigmine use along with their possible mechanisms are listed in the Table.

Nonpharmacologic management of an overdose of an anticholinergic drug is possible and includes gastric lavage, close monitoring of vital signs, bowel sounds, pupillary size, and mental status. Also, of course,

(continued)

Table—Contraindications to Physostigmine

Condition	Possible Mechanism
Diabetes	Parasympathetic stimulation of insulin secretion
Gangrene	Sympathetic vasoconstriction
Renal hypertension; coronary artery disease	Sympathetic elevation of blood pressure
Heart block	Parasympathetic decrease in conduction velocity
Cardiac arrhythmia	Sympathetic increase in automaticity of idiopathic pacing mechanisms
Hypothyroidism	Parasympathetic cardiac effects
Hyperthyroidism	Increased sympathetic tone
Bronchitis; asthma	Parasympathetic bronchial gland secretion; bronchial smooth muscle contraction
Peptic ulcer	Parasympathetic gastric acid secretion
Colitis	Parasympathetic increased smooth muscle contraction
Urinary or renal obstruction	Parasympathetic increased smooth muscle contraction
Glaucoma	Dilation of fine blood vessels with increased permeability of the blood-aqueous humor barrier, worsening intraocular pressure[10]
Pregnancy	Increased smooth muscle contraction
Myotonia atrophica or congenita	Cholinomimetic action of some anticholinesterase agents can increase muscle contraction
Vagotonia	Parasympathetic stimulation

careful behavioral management should include reassuring and informing the patient, who should be placed in a protected and quiet environment. If a serious overdose is suspected, the patient should be admitted to an intensive care unit with cardiac monitoring because of the possibility of late-developing tachyarrhythmias. Serious anticholinergic overdoses are often associated with durations of the QRS segment of the electrocardiogram of greater than 100 milliseconds.[12]

In the case of the frankly delirious patient who must be controlled with medication and for whom there is some suspicion that an anticholinergic agent such as PCP may have been ingested, one of the benzodiazepines is the agent of choice. Diazepam can be given in doses of 5 to 10 mg four times a day. As a precautionary measure, when multiple medications must be prescribed, a combination of drugs having marked anticholinergic properties should be avoided. This may be a consideration in the choice of one phenothiazine or another; generally those with strong anticholinergic properties are contraindicated when used with other strongly anticholinergic drugs.

Conclusion

The central anticholinergic syndrome can present in many clinical situations in a less than clear fashion. If a high index of suspicion is maintained, however, the physician is likely to recognize the syndrome. Support, observation, and verbal reassurance may be sufficient treatment in many cases, but physostigmine is generally considered the agent to be used for diagnostic and therapeutic purposes. Cautioning patients and their families about the use of over-the-counter medications, especially for patients already taking anticholinergic drugs, may be of value. As the index of suspicion for this not infrequent syndrome increases, better diagnostic acumen and treatment skills result. □

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