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Nicotiana glauca (Tree Tobacco) Intoxication—Two Cases in One Family

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Abstract We present two cases of rare human poisoning in one family following ingestion of cooked leaves from the tobacco tree plant, *Nicotiana glauca*. The toxic principle of *N. glauca*, anabasine (C10H14N2), is a small pyridine alkaloid, similar in both structure and effects to nicotine, but appears to be more potent in humans. A 73-year-old female tourist from France, without remarkable medical history, collapsed at home following a few hours long prodrome of dizziness, nausea, vomiting, and malaise. The symptoms developed shortly after eating *N. glauca* cooked leaves that were collected around her daughter's house in Jerusalem and mistaken for wild spinach. She was found unconscious, with dilated pupils and extreme bradycardia. Following resuscitation and respiratory support, circulation was restored. However, she did not regain consciousness and died 20 days after admission because of multi-organ failure. Anabasine was identified by gas chromatography/mass spectrometry method in *N. glauca* leaves and in the patient's urine. Simultaneously, her 18-year-old grandson developed weakness and myalgia after ingesting a smaller amount of the same meal. He presented to the same emergency room in a stable condition. His exam was remarkable only for sinus bradycardia. He was discharged without any specific treatment. He recovered in 24 h without any residual sequelae. These cases raise an awareness of the potential toxicity caused by ingestion of tobacco tree leaves and highlight the dangers of ingesting botanicals by lay public. Moreover, they add to the clinical spectrum of *N. glauca* intoxication.

Keywords *Nicotiana glauca* · Tobacco tree · Nicotine · Anabasine · Poisoning · Gas chromatography · Mass spectrometry

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Introduction

Nicotine is a pyridine alkaloid derived from the tobacco plant (*Solanacea* family, *Nicotiana* genus). First identified in 1826, it is named after Jean Nicot (1530–1600), a French diplomat, who is believed to have introduced snuff-powdered tobacco to Europe. *Nicotiana glauca* Grah, also known as wild tobacco or tree tobacco, is a multi-branched perennial shrub of up to 5 m high with smooth green hairless branches, glaucous leaves, and tubular yellow flowers (Fig. 1) [1]. *Glauca* was derived from the Greek meaning "bluish-gray", referring to the powdery coating on this plant. Leaves of the *N. glauca* are large, alternate, ovate, and blue-green in color with a powdery coating, and are smoked for ritual purposes by Navajo Indians. *N. glauca* is indigenous to South America. It has been widely introduced and naturalized in the warm dry climates, and has become a weed plant in Arizona, California, Texas, Mexico, Hawaiian Islands, the Mediterranean region, and Australia. In Israel, the plant is found along walls, on debris or growing along sandy areas.

Fig. 1 A structural nicotine analog

Species in the genus *Nicotiana* are characterized by the presence of pyridine alkaloids in leaf and root tissues, the four most abundant being nicotine, nornicotine, anabasine, and anatabine [2]. Anabasine ($C_{10}H_{14}N_2$), a structural nicotine analog (Fig. 2), constitutes a significant proportion (98%) of the alkaloids in only a few species, among them *N. glauca* [2, 3]. Its content varies among various parts of the plant, being highest in the leaves and the bark. This highly toxic alkaloid is responsible for the clinical toxicology of the plant: teratogenic effects caused by consumption of *N. glauca* in animals [4–7] and either severe [8–13] or fatal poisoning in humans [8, 12, 14–16]. In most of these cases the patients mistook the plant for an edible green (such as marog—*Amaranthus hybridus*, *Amranthaceae*, spinach—*Spinacia oleracea*, or pokeweed—*Phytolacca americana*).

Anabasine is a nicotinic receptor agonist that exerts its clinical effect primarily by binding to nicotinic acetylcholine receptors at the neuromuscular junction, autonomic ganglia and brain. It is less potent compared with (−) nicotine based on in vitro and animal studies [17, 18]. In *N. glauca*, anabasine exists as a racemic mixture of S and R enantiomers, with R-anabasine being somewhat more potent compared with S-anabasine [19]. Anabasine was also found to be a weak inhibitor of acetylcholinesterase (I_{50} of 1,000 μM) [20]; however, the main clinical

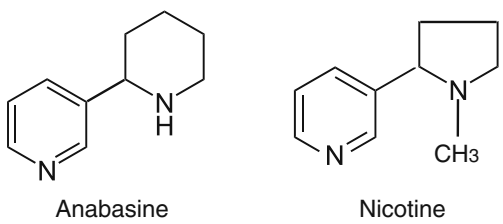

Fig. 2 Chemical structures of anabasine and nicotine

effects of its toxicity are caused by neuromuscular blockade [9].

We report two cases of the rare human poisoning by ingested cooked tobacco tree leaves in one family, confirmed by gas chromatography/mass spectrometry analysis, and discuss the difference in clinical manifestations and the time course in both cases. Literature review of 16 cases of *N. glauca* intoxication is provided to better characterize the time course, clinical presentation, and outcomes of this uncommon intoxication.

Case 1

A 73-year-old female tourist from France born in Algeria, without any remarkable medical history, came to visit her daughter's family in Jerusalem, Israel. The family was living in a new neighborhood with building debris around the house. Upon her arrival, she found green shrubs with glaucous leaves around the neighborhood that she mistook for spinach. She collected the leaves and cooked a dish according to the recipe that she recalled from her childhood. Approximately 30 min following the meal, she complained of being unwell and said to her family that she might have food poisoning. She vomited several times and went to rest. Vomiting recurred 90 min later, followed by loss of consciousness. In a few minutes, a neighbor physician started cardiopulmonary resuscitation (CPR). He reported that on his exam the patient was unconscious, gasping, central pulse was 30 beats/min, and she had dilated pupils. A paramedic team that arrived 5 min later reported that the patient was not breathing, and no pulse was palpated. Cardiac monitor showed pulseless electrical activity. The patient was cyanotic, and her periphery was cold. The patient was intubated. Following advanced cardiac life support for 5 min that included repeated administration of adrenaline and atropine, she had restored systolic blood pressure of 100 mmHg and sinus rhythm on monitor. The patient was transferred to Shaare Zedek Medical Center, Jerusalem. On examination at the Emergency Department (ED), the patient remained unconscious and unresponsive to painful stimuli. She was intubated and ventilated, her blood pressure was 125/75 mmHg, PR 80 beats/min, and temperature was 35.7°C. The pupils were dilated and unresponsive. There were no localizing signs on neurological exam. There was no muscle fasciculation. The rest of the physical exam revealed bi-basilar inspiratory crackles, regular heart sounds, soft abdomen without organomegaly, and no peripheral edema. Initial laboratory blood work up at the ED showed complete blood count remarkable for leukocytosis (WBC 19,000/μl, polymorphonuclears 68%), along with normal electrolytes and renal panel (Na 139 mEq/L, K 3.6 mEq/L, BUN 18 mg/dL, creatinine 0.8 mg/dL). Arterial blood gas analysis was notable for combined metabolic and respiratory acidosis

(pH 7.11, pCO2 60 mmHg, pO2 64 mmHg, HCO3 15 mEq/L). Creatine phosphokinase was mildly elevated (238 IU/L). Liver enzymes drawn about 4 h later were significantly elevated (aspartate aminotransferase (AST) 821 IU/L, alanine aminotransferase (ALT) 569 IU/L, lactate dehydrogenase (LDH; 4,300 IU/L). Within 24 h, a downtrend of liver enzymes was observed (AST declined to 152 IU/L, ALT to 238, and LDH to 1,160). Urinary toxicology screen was negative. To exclude digitalis intoxication, digoxin plasma level was obtained and found to be negative. Chest X-rays demonstrated a diffuse infiltrate in the right lung, consistent with aspiration. Head computed tomography did not reveal any focal finding. On the first hospitalization day, the patient's family gathered a sample of the culprit plant and it was taken to the Botanical Department at the Hebrew University in Jerusalem. A botanist had identified the plant as *N. glauca*. To confirm anabasine-induced intoxication, the leaves of the plant and patient's urine sample were sent to gas chromatography/mass spectrometry analysis that eventually confirmed significant anabasine content in both specimens. The patient did not regain consciousness because of anoxic brain damage. She died 20 days after admission because of infectious complications and multi-organ failure.

Case 2

Simultaneously, an 18-year-old grandson of the aforementioned patient developed general weakness and myalgia a few hours after ingesting a smaller amount of the same meal. He presented to the same ED in a stable condition. He was afebrile. His physical exam was remarkable only for sinus bradycardia (50 beats/min). Blood work up was not performed. He was discharged without any specific treatment. He reported dizziness, fatigue, and headache that had resolved spontaneously in 24 h without any residual sequellae.

Discussion

N. glauca is atypical within the genus *Nicotiana*, in that anabasine ($C_{10}H_{14}N_2$) rather than nicotine is predominant as the main component of its leaf pyridine alkaloid fraction [2, 3]. Anabasine has been identified as the responsible teratogen of *N. glauca* in animals [4–7] and poisoning agent in humans [8–16]. Poisoning by anabasine is characterized by nicotine-like toxicity. The clinical effects of nicotine alkaloid toxicity are the result of the summation of actions at ganglionic sites, motor end plates, and smooth muscle [17, 18, 21–23]. Nicotine alkaloids initially stimulate the ganglia of the sympathetic and parasympathetic nervous systems by direct cholinomimetic action on the ganglia. This is quickly followed by prolonged ganglionic blockage due to persistent depolarization. A similar action occurs at the neuromuscular junction causing total paralysis of skeletal muscles and subsequent respiratory failure. The CNS is affected initially by stimulation, resulting in tremors and convulsions, progressing to depression. Death occurs from respiratory failure due to peripheral blockage of the muscles of respiration. Vomiting is a result of stimulation of the emetic chemoreceptor trigger zone [10]. Additionally, patients exposed to substantial amounts of nicotine alkaloid may have tachycardia and hypertension. Cardiovascular collapse can follow the hypertension depending on the degree of toxic exposure [18]. Stimulation of sympathetic ganglia and the adrenal medulla combined with discharge of catecholamines from sympathetic nerve endings and chromaffin tissues of different organs are postulated to be responsible for the cardiovascular signs.

High-performance liquid chromatography/photodiode array/mass spectrometry (HPLC/PDA/MS) has been used to detect and quantify anabasine [12, 14–16]. Based on postmortem analysis of blood nicotine and anabasine concentrations in the fatal poisoning cases in humans, anabasine was suggested to be more toxic compared with nicotine. The blood concentration of anabasine found in a fatally poisoned young man was 1.15 mg/L [14] and 2.2 mg/L in a 43-year-old male who died after an apparent ingestion of *N. glauca* water extract [15]. Tissue levels of anabasine detected in the former fatal case [14] were as following: urine, 73.8 mg/L; kidney, 15.8 mg/kg; brain, 11.0 mg/kg; lung, 10.5 mg/kg; heart, 10.4 mg/kg; and gastric contents, 113.4 mg/L. In comparison, the reported fatal ingestions of nicotine doses of 10 to 25 g were associated with blood concentrations ranging from 11 to 63 mg/L [24].

The onset of symptoms in an acute nicotine alkaloid poisoning is usually rapid, within 15–30 min of ingestion and the symptoms often follow a biphasic pattern with initial vomiting and adrenergic stimulation followed by symptoms of ganglionic and neuromuscular blockage [22, 23]. The present case is consistent with this pattern of nicotinic intoxication with vomiting and dizziness developing 30 min after ingestion, followed by a respiratory arrest after about 90 min. There is no antidote for nicotinic cholinergic poisoning, and the treatment is largely supportive and symptomatic [17, 18].

There are very few reports in the literature of verified *N. glauca* toxicity in humans. One possible explanation for the small number of the reports is that most cases of mild poisoning do not present to a medical attention, whereas others could have been underdiagnosed and/or underreported. The available details from all the published case reports have been summarized in Table 1.

Our cases and an analysis of the published literature demonstrate several key features in the presentation of *N. glauca* poisoning. In the majority of the cases, the victims seemed to misidentify the plant for another familiar edible

Table 1 *N. glauca* literature review of poisoning cases in humans

Patient data	Event date and reference	Geographical location	How poisoned	Time interval from exposure to symptoms onset	Clinical manifestations on presentation	Dx confirmation	Outcome
F, 7 years old	1962 [8]	USA, California	Ingestion of boiled tobacco leaves	Not reported	Not reported	Local taxonomist (LA Botanical Garden)	Death
F, adult	1962 [8]	USA, California	Ingestion of boiled tobacco leaves	Not reported	Not reported	Local taxonomist (LA Botanical Garden)	Recovery
F, child	1962 [8]	USA, California	Ingestion of boiled tobacco leaves	Not reported	Not reported	Local taxonomist (LA Botanical Garden)	Recovery
M, AA, 76 years old	1983 [10]	USA, California	Ingestion of the leaves	1–1.5 h	Weakness, ataxia, sweating, muscle twitching, loss of consciousness	Consultants at the San Diego Museum of Natural History	Recovery with supportive care
M, young adult	1987 [14]	USA, San Diego, Ca	Ingestion of the leaves	Not reported	Found dead	GC/MS of leaves and post mortem analysis of body tissue and fluids	Death
F, 50 years old	1997 [11]	Australia	Ingestion of 3 steamed tobacco leaves	1 h (initial sxs); 5 h—neurologic sxs	Blurred vision; bloating, diarrhea; involuntary jerking of the lower limbs and ataxia; tremor	Consultant at the Adelaide Botanic Garden	Recovery after 24 h with ventilatory support
M, Thai, 52 years old	1999 [12]	Israel	Ingestion (small amount of leaves)	Few minutes: vomiting; 2 h from ingestion: full presentation	Nausea, vomiting, headache	GC/MS of leaves	Recovery with supportive tx
M, Thai, 46 years old	1999 [12]	Israel	Ingestion (large amount of leaves)	2 h	Nausea, vomiting, hypersalivation, headache, fever, palpitations, hypertension; cardiac arrest	GC/MS of leaves, food extract, blood and urine	Death
M, White, 60 years old	1999 [9]	USA, Georgia	Ingestion of 10–12 fried leaves	5 min—mild sxs; 3 h—severe muscle weakness	Dizziness; mild weakness, diaphoresis, nausea, vomiting; watery diarrhea; Severe muscle weakness	Botanist University of California at Riverside	Recovery with supportive tx
M, AA, 37 years old	1999 [9]	USA, Georgia	Ingestion of leaves	4 h—initial sxs; 9 h—full paralysis	Generalized weakness, "stifffeeling jaw", double vision; profound generalized muscle weakness[a]	Local botanist	Recovery with supportive tx
M, 43 years old	1999 [15]	Australia	Ingestion of water extract of *N. glauca*	Not reported	Found dead	GC/MS of water extract and post mortem analysis of body andtissues fluids	Death
F, elderly	2002 [16]	South Africa, Johannesburg	Ingestion of cooked leaves	Not reported	Not reported	HPLC	Death
M, young	2002 [16]	South Africa, Johannesburg	Ingestion of cooked leaves	Not reported	Not reported	HPLC	Death
F, Latina, 3 months old	2006 [13]	USA, California	Dermal absorption (application of a leaf to baby's abdomen) –remedy folk	8 h	Progressive respiratory failure, flaccid paralysis	Liquid chromatography/MS in the leaf and urine; anatabine identified in the urine	Full recovery in 36 h
F, 73 years old	Furer 2010	Israel, Jerusalem	Ingestion of cooked leaves	30 min—first manifestation; ~ 2 h—collapse	Nausea, vomiting, dizziness. Respiratory failure	GC/MS of leaves and urine sample	Death
M, 18 years old	Furer 2010	Israel, Jerusalem	Ingestion of cooked leaves (small amount)	~2–3 h	Generalized weakness, myalgia, bradycardia	GC/MS of leaves	Spontaneousrecovery in 24 h

Abbreviations: *AA* African American, *dx* diagnosis, *exp* exposure, *F* female, GC/*MS* gas chromatography/mass spectrometry, *HPLC* high-performance liquid chromatography, *h* hours, *M* male, *min* minutes, *sxs* symptoms, *tx* treatment

[a] Drug screen was positive for cannabinoid

green. Toxicity had mainly resulted from anabasine ingestion that was confirmed in nine cases by HPLC/PDA/MS methods [12–16]. However, our review implies a key role for the botanist's support that allowed a quick and reliable identification of the leaves morphology and therefore diagnosis. Importantly, one pediatric case of a topical application of the tobacco tree leave as a folk remedy demonstrated that anabasine toxicity can result from dermal exposure and absorption in addition to gastric absorption [13].

The onset of symptoms ranged from 5 min to 3 h after ingestion. Out of 15 reported cases, seven resulted in death. The symptoms ranged from nausea, vomiting, palpitations and weakness to muscle paralysis, cardiovascular collapse, and respiratory failure.

Remarkably, elevated liver enzymes (AST, ALT, and LDH) drawn about 6 h after arrest were observed in our first case. Given a disproportional elevation of LDH compared with AST and ALT, and a significant downtrend of the enzymes within 24 h, these abnormalities were interpreted as ischemic hepatitis rather than direct anabasine hepatotoxicity. Supporting this notion, no evidence of hepatotoxicity was found in three other cases that had recovered from anabasine intoxication [9–11]. Autopsy findings in a fatal case caused by *N. glauca* ingestion revealed essentially normal internal organs, except for a minor nonspecific focal polymorph infiltrate in the liver [15].

The cases we described demonstrate a variability of clinical presentation from mild symptoms to fatal outcome, probably due to a difference in the ingested amount of the poisonous plant. Importantly, limitations of our second case should be noted. Whereas history of *N. glauca* leaves ingestion by the grandson seemed to be reliable, it was not confirmed by testing of gastric content or tissues anabasine level. Non-specific clinical manifestations (such as general weakness, myalgia, and sinus bradycardia) might represent other medical conditions, such as a psychosomatic response to observing a close family member unexpected collapse. Therefore, no definitive conclusion regarding the dose dependent effect of *N. glauca* induced intoxication can be drawn from our cases.

Conclusion

Ingestion of *N. glauca* leaves or their extract has a toxic potential. The toxicity is mediated by nicotine-like alkaloid, anabasine. This poisoning should be included in the differential diagnosis of sudden onset of muscle paralysis and respiratory arrest.

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