Arsenic poisoning

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Arsenic poisoning interferes with cellular longevity by allosteric inhibition of an essential metabolic enzyme pyruvate dehydrogenase (PDH) complex which catalyzes the reaction Pyruvate + CoA-SH + NAD+ PDH Acetyl-Co-A + NADH + CO_2. With the enzyme inhibited, the energy system of the cell is disrupted resulting in a cellular apoptosis episode. Biochemically, arsenic prevents use of thiamine resulting in a clinical picture resembling thiamine deficiency. Poisoning with arsenic, can raise lactate levels and lead to lactic acidosis. Arsenic in cells clearly stimulates the production of hydrogen peroxide (H_2O_2). When the H_2O_2 reacts with Fenton metals such as iron, it produces a highly reactive hydroxyl radical. Inorganic Arsenic trioxide found in ground water particularly affects Voltage-gated potassium channels , [1] disrupting cellular electrolytic function resulting in neurological disturbances, cardiovascular episodes such as prolonged qt interval, high blood pressure [2] central nervous system dysfunction and death. Arsenic trioxide is a ubiquitous element present in American drinking water. [3]

Arsenic poisoning

Classification and external resources

ICD-10	T57.0 (http://apps.who.int/classifications/apps/icd/icd10online/?gt51.htm+t570)
ICD-9	985.1 (http://www.icd9data.com/getICD9Code.ashx?icd9=985.1)
eMedicine	emerg/42 (http://www.emedicine.com/emerg/topic42.htm)
MeSH	D020261 (http://www.nlm.nih.gov/cgi/mesh/2010/MB_cgi?field=uid&term=D020261)

> “Arsenic exposure plays a key role in the pathogenesis of vascular endothelial dysfunction as it inactivates endothelial nitric oxide synthase, leading to reduction in the generation and bioavailability of nitric oxide. In addition, the chronic arsenic exposure induces high oxidative stress, which may affect the structure and function of cardiovascular system. Further, the arsenic exposure has been noted to induce atherosclerosis by increasing the platelet aggregation and reducing fibrinolysis. Moreover, arsenic exposure may cause arrhythmia by increasing the QT interval and accelerating the cellular calcium overload. The chronic exposure to arsenic upregulates the expression of tumor necrosis factor-α, interleukin-1, vascular cell adhesion molecule and vascular endothelial growth factor to induce cardiovascular pathogenesis.”

—Pitchai Balakumar1 and Jagdeep Kaur, "Arsenic Exposure and Cardiovascular Disorders: An Overview", *Cardiovascular Toxicology*, December 2009[4]

Contents

Toxicity

The toxicity of arsenic and its compounds is not highly variable[5]. Organic forms appear to have a lower toxicity than inorganic forms of arsenic. Research has shown that the arsenites (trivalent forms) in drinking water have a higher acute toxicity than arsenates (pentavalent forms).[6] The acute minimal lethal dose of arsenic in adults is estimated to be 70 to 200 mg or 1 mg/kg/day.[7] Most reported arsenic poisonings are not caused by elemental arsenic, but by one of arsenics compounds, found in drinking water, arsenic trioxide which is 500 times more toxic than pure arsenic. Symptoms include changes in respiration, tachycardia and hypertension with headaches and lightheadedness, which if chronic and untreated will result in damage to the kidneys, heart, brain or even death.

Arsenic is suspiciously related to the first five leading causes of non accidental death in the United States. Bringing the total to 1,525,675 related mortalities. EPA efforts are underway to reduce drinking water exposure to zero. [8] Lead causes of mortality in the world are all related to Arsenic. These are [9] Heart disease [10] (hypertension related cardiovascular), Cancer, [11] stroke [12] (cerebrovascular diseases) Chronic lower respiratory diseases, [13] and Diabetes. These diseases are all related to the alteration of voltage dependent potassium channels. Researchers, led by Ana Navas-Acien, MD, PhD, of the Johns Hopkins Bloomberg School of Health, studied 788 adults who had their urine tested for arsenic exposure in the 2003-2004 National Health and Nutrition Examination Survey. Participants with type 2 diabetes had a 26% higher level of total arsenic in their urine than those without the disease. Diabetes is also related to alteration of voltage dependent potassium channels due in part to the function of insulin and potassium in the cellular metabolism of glucose. Due to the regular appearance of Arsenic in public drinking water supplies, it is likely that Arsenic plays a part in about thirty percent of total all cause mortality in America. Arsenic prevalence in the water has been related to the occurrence of hypertension, erectile dysfunction and related conditions.

Chronic exposure to inorganic arsenic may lead to Hypertension, involuntary muscular dysfunction (including incontinence), diabetes, neuropathy, depression, obesity and any other condition related to the altered role of intercellular voltage dependent potassium channels, including cutaneous hyperpigmentation.[14]:859

Pathophysiology

Main article: Arsenic toxicity

Tissue culture studies have shown that arsenic blocks both IKr and Iks channels and, at the same time, activates IK-ATP channels. Arsenic also disrupts ATP production through several mechanisms. At the level of the citric acid cycle, arsenic inhibits pyruvate dehydrogenase and by competing with phosphate it uncouples oxidative phosphorylation, thus inhibiting energy-linked reduction of NAD+, mitochondrial respiration, and ATP synthesis. Hydrogen peroxide production is also increased, which might form reactive oxygen species and oxidative stress. These metabolic interferences lead to death from multi-system organ failure, probably from necrotic cell death, not apoptosis. A post mortem reveals brick red colored mucosa, due to severe hemorrhage. Although arsenic causes toxicity, it can also play a protective role.[15]

Diagnosis

There are tests available to diagnose poisoning by measuring arsenic in blood, urine, hair, and fingernails. The urine test is the most reliable test for arsenic exposure within the last few days. Urine testing needs to be done within 24–48 hours for an accurate analysis of an acute exposure. Tests on hair and fingernails can measure exposure to high levels of arsenic over the past 6–12 months. These tests can determine if one has been exposed to above-average levels of arsenic. They cannot predict, however, whether the arsenic levels in the body will affect health.[16]

Hair is a potential bioindicator for arsenic exposure due to its ability to store trace elements from blood. Incorporated elements maintain their position during growth of hair. Thus for a temporal estimation of exposure, an assay of hair composition needs to be carried out with a singe hair which is not possible with older techniques requiring homogenization and dissolution of several strands of hair. This type of biomonitoring has been achieved with newer microanalytical techniques like Synchroton radiation based X ray fluorescence (SXRF) spectroscopy and Microparticle induced X ray emission (PIXE).The highly focused and intense beams study small spots on biological samples allowing analysis to micro level along with the chemical speciation. In a study, this method has been used to follow arsenic level before, during and after treatment with Arsenious oxide in patients with Acute Promyelocytic Leukemia.[17].

Treatment

Chemical and synthetic methods are now used to treat arsenic poisoning. Dimercaprol and dimercaptosuccinic acid are chelating agents which sequester the arsenic away from blood proteins and are used in treating acute arsenic poisoning. The most important side-effect is hypertension. Dimercaprol is considerably more toxic than succimer.[18]

In the journal *Food and Chemical Toxicology*, Keya Chaudhuri of the Indian Institute of Chemical Biology in Kolkata, and her colleagues reported giving rats daily doses of arsenic in their water, in levels equivalent to those found in groundwater in Bangladesh and West Bengal. Those rats which were also fed garlic extracts had 40 percent less arsenic in their blood and liver, and passed 45 percent more arsenic in their urine. The conclusion is that sulfur-containing substances in garlic scavenge arsenic from tissues and blood. The presentation concludes that people in areas at risk of arsenic contamination in the water supply should eat one to three cloves of garlic per day as a preventative.[19][20][21]

Unintentional poisoning

In addition to its presence as a poison, for centuries arsenic was used medicinally. In China, it has been used for over 2,400 years as a part of it traditional Chinese medicine.[22] In the western world, Arsenic was used extensively to treat syphilis before penicillin was introduced. It was eventually replaced as a therapeutic agent by sulfa drugs and then by antibiotics. Arsenic was also an ingredient in many tonics (or "patent medicines").

In addition, during the Victorian era, some women used a mixture of vinegar, chalk, and arsenic applied topically to whiten their skin. This use of arsenic was intended to prevent aging and creasing of the skin, but some arsenic was inevitably absorbed into the blood stream.

Some pigments, most notably the popular Emerald Green (known also under several other names), were based on arsenic compounds. Overexposure to these pigments was a frequent cause of accidental poisoning of artists and craftsmen. One of the biggest unintentional cases of arsenic poisoning via well water consumption is in Bangladesh and called by the World Health Organization as the “largest mass poisoning of a population in history.”[23]

Occupational exposures

Industries that use inorganic arsenic and its compounds include wood preservation, glass production, nonferrous metal alloys, and electronic semiconductor manufacturing. Inorganic arsenic is also found in coke oven emissions associated with the smelter industry.[24]

Occupational exposure to arsenic may occur with copper or lead smelting and wood treatment, among workers involved in the production or application of pesticides containing organic arsenicals. Humans are exposed to arsenic through air, drinking water, and food (meat, fish, and poultry); poultry is usually the largest source of food-based arsenic ingestion due to usage of certain antibiotics in chicken feed. Arsenic was also found in wine if arsenic pesticides are used in the vineyard. Arsenic is well absorbed by oral and inhalation routes, widely distributed and excreted in urine; most of a single, low-level dose is excreted within a few days after consuming any form of inorganic arsenic. Remains of arsenic in nails (which show as white spots and lines) and hair can be detected years after the exposure.

Arsenicosis: chronic arsenic poisoning from drinking water

Main article: Arsenic contamination of groundwater

Chronic arsenic poisoning results from drinking water with arsenic over a long period of time. This may occur due to arsenic contamination of groundwater.[25] The World Health Organization recommends a limit of 0.01 mg/L (10ppb) of arsenic in drinking water. This recommendation was established based on the limit of detection of available testing equipment at the time of publication of the WHO water quality guidelines. More recent findings show that consumption of water with levels as low as 0.00017 mg/L (0.17ppb) over long periods of time can lead to arsenicosis.[*citation needed*]

From a 1988 study in China, the US protection agency quantified the lifetime exposure of arsenic in drinking water at concentrations of 0.0017 mg/L, 0.00017 mg/L, and 0.000017 mg/L are associated with a lifetime skin cancer risk of 1 in 10,000, 1 in 100,000, and 1 in 1,000,000 respectively. The World Health Organization contends that a level of 0.01 mg/L poses a risk of 6 in 10000 chance of lifetime skin cancer risk and contends that this level of risk is acceptable.[26] Any search of physician periodicals on-line will yield considerable evidence that arsenic is linkable to the onset of leading causes of death in the world's all cause mortality statistics as compiled by the World Health Organization.

Intentional poisoning

Arsenic became a favorite murder weapon of the Middle Ages and Renaissance, particularly among ruling classes in Italy, notably the Borgias. Because the symptoms are similar to those of cholera, which was common at the time, arsenic poisoning often went undetected. By the 19th C., it had acquired the nickname "inheritance powder," perhaps because impatient heirs were known or suspected to use it to ensure or accelerate their inheritances.

In ancient Korea, and particularly in Joseon Dynasty, arsenic-sulfur compounds have been used as a major ingredient of *sayak* (사약; 賜藥), which was a poison cocktail used in capital punishment of high-profile political figures and members of the royal family.[27] Due to social and political prominence of the condemned, many of these events were well-documented, often in the Annals of Joseon Dynasty; they are sometimes portrayed in historical television miniseries because of their dramatic nature.[28]

On April 27, 2003, sixteen members of the Gustaf Adolph Lutheran Church in New Sweden, Maine, became ill following the church coffee hour; one man, Reid Morrill, died a short time later. It was found that the coffee had been heavily laced with arsenic, setting off a flurry of local gossip and hysteria and worldwide media coverage. As of the 2005 publication of journalist Christine Young's book, *A Bitter Brew*, no one had been charged with the crime, but Young's book revealed that lifelong church member Daniel Bondeson, who shot himself at his family farm five days after the poisoning, left a note confessing sole responsibility for the crime. Bondeson died while undergoing surgery, leaving Maine State Police and many church members convinced someone had helped Bondeson, Young's book rejected the conspiracy theory, citing evidence that the well-liked Bondeson had a dark side, harboring bitter grudges and battling emotional problems. In 2006, the Maine Attorney General agreed that Bondeson had acted alone and closed the case.

Murder mystery stories often feature arsenic poisoning, although they commonly omit the more disagreeable symptoms.

Detection in biological fluids

Arsenic may be measured in blood or urine to monitor excessive environmental or occupational exposure, confirm a diagnosis of poisoning in hospitalized victims or to assist in the forensic investigation in a case of fatal overdosage. Some analytical techniques are capable of distinguishing organic from inorganic forms of the element. Organic arsenic compounds tend to be eliminated in the urine in unchanged form, while inorganic forms are largely converted to organic arsenic compounds in the body prior to urinary excretion. The current biological exposure index for U.S. workers of 35 μg/L total urinary arsenic may easily be exceeded by a healthy person eating a seafood meal.[29]

Famous victims (known and alleged)

Arsenic poisoning, accidental or deliberate, has been implicated in the illness and death of a number of prominent people throughout history.

Francesco I de' Medici, Grand Duke of Tuscany

Recent forensic evidence uncovered by Italian scientists suggests that Francesco and his wife were poisoned possibly by his brother and successor Fernando.[30]

George III of Great Britain

George III's (1738 – 1820) personal health was a concern throughout his long reign. He suffered from periodic episodes of physical and mental illness, five of them disabling enough to require the King to withdraw from his duties. In 1969, researchers asserted that the episodes of madness and other physical symptoms were characteristic of the disease porphyria, which was also identified in members of his immediate and extended family. In addition, a 2004 study of samples of the King's hair[31] revealed extremely high levels of arsenic, which is a possible trigger of disease symptoms. A 2005 article in the medical journal The Lancet[32] suggested the source of the arsenic could be the antimony used as a consistent element of the King's medical treatment. The two minerals are often found in the same ground, and mineral extraction at the time was not precise enough to eliminate arsenic from compounds containing antimony.

Napoleon Bonaparte

It has been theorized that Napoleon Bonaparte (1769 – 1821) suffered and died from arsenic poisoning during his imprisonment on the island of Saint Helena. Forensic samples of his hair did show high levels, 13 times the normal amount, of the element. This, however, does not prove deliberate poisoning by Napoleon's enemies: copper arsenite has been used as a pigment in some wallpapers, and microbiological liberation of the arsenic into the immediate environment would be possible. The case is equivocal in the absence of clearly authenticated samples of the wallpaper. As Napoleon's body lay for nearly 20 years in a grave on the island, before being moved to its present resting place in Paris, arsenic from the soil could not have polluted the sample as the arsenic was found within his hair, which can only be possible when the arsenic was already in the body. Even without contaminated wallpaper or soil, commercial use of arsenic at the time provided many other routes by which Napoleon could have consumed enough arsenic to leave this forensic trace.

Charles Francis Hall

American explorer Charles Francis Hall (1821–1871) died unexpectedly during his third Arctic expedition aboard the ship *Polaris*. After returning to the ship from a sledging expedition Hall drank a cup of coffee and fell violently ill.[33] He collapsed in what was described as a fit. He suffered from vomiting and delirium for the next week, then seemed to improve for a few days. He accused several of the ship's company, including ship's physician Dr. Emil Bessels with whom he had longstanding disagreements, of having poisoned him.[33] Shortly thereafter, Hall again began suffering the same symptoms, died, and was taken ashore for burial. Following the expedition's return a US Navy investigation ruled that Hall had died from apoplexy.[34]

In 1968, however, Hall's biographer Chauncey C. Loomis, a professor at Dartmouth College, traveled to Greenland to exhume Hall's body. Due to the permafrost, Hall's body, flag shroud, clothing and coffin were remarkably well preserved. Tissue samples of bone, fingernails and hair showed that Hall died of poisoning from large doses of arsenic in the last two weeks of his life,[35] consistent with the symptoms party members reported. It is possible that Hall dosed himself with quack medicines which included the poison, but it is more likely that he was murdered by Dr. Bessels or one of the other members of the expedition.[36]

Huo Yuan Jia

Huo Yuan Jia made his name as a Chinese martial artist. There was rumour that he was poisoned in 1910.

Clare Boothe Luce

A later case of arsenic poisoning is that of Clare Boothe Luce, (1903 – 1987) the American ambassador to Italy 1953–1956. Although she did not die from her poisoning, she suffered an increasing variety of physical and psychological symptoms until arsenic poisoning was diagnosed, and its source traced to the old, arsenic-laden flaking paint on the ceiling of her bedroom. Another source (see below) explains her poisoning as resulting from eating food contaminated by flaking of the ceiling of the embassy dining room.

Impressionist painters

Emerald Green, a pigment frequently used by Impressionist painters, is based on arsenic. Cézanne developed severe diabetes, which is a symptom of chronic arsenic poisoning. Monet's blindness and Van Gogh's neurological disorders could have been partially due to their use of Emerald Green. Poisoning by other commonly used substances, including liquor and absinthe, lead pigments, mercury-based Vermilion, and solvents such as turpentine, could also be a factor in these cases.

The Emperor Guangxu

Recent testing in the People's Republic of China has confirmed that China's second-to-last emperor was poisoned with a massive dose of arsenic; suspects include his dying aunt, the Empress Dowager Cixi, and her strongman, Yuan Shikai.

Phar Lap

The famous and largely successful New Zealand racehorse Phar Lap died suddenly in 1932. Poisoning was considered as a cause of death and several forensic examinations were completed at the time of death. In a recent examination, 75 years after his death, forensic scientists determined that the horse had ingested a massive dose of arsenic shortly before his death.[37] However, professional opinions are mixed as to whether or not the arsenic compound caused the animal's final illness and death.

See also

- Forensic toxicology
- 2007 Peruvian meteorite event - a meteorite impact that is believed to have caused arsenic poisoning.
- James Marsh was a chemist, who invented the Marsh test for detecting arsenic.
- Arsine is a compound of Arsenic that is highly toxic and dangerously flammable.

Footnotes

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External links

- Arsenic poisoning (http://www.dmoz.org/Science/Environment/Environmental_Health/Toxic_Substances/Arsenic//) at the Open Directory Project
- Subterranean Arsenic Removal (SAR) Technology in West Bengal (http://www.insituarsenic.org)
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