TOXICITY

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OBJECTIVE :

- Define minerals toxicity
- Outline the difference between toxic mineral & mineral toxicity
- List with examples the clinically important disorders that result from minerals toxicity

POISON

- **A poison : defined as any substance that cause a harmful effect on exposure.**
- **The concept that any substance has a potential to cause harm if given at the correct dosage (even water) is a central theme in toxicology .**

BASIC CONCEPT

- 1- Is the metal of concern toxic ?
- 2- What is the prevalence associated with the metal of concern ?
- 3- What is the sign and symptoms of exposure to that metal ?
- 4- Is the degree of exposure known?
- 5- Do educate analytical techniques exist to measure this metal?

DIAGNOSING TOXICITY

- Diagnosing of metal toxicity requires demonstration of all of the following factors:
- 1- A source of metal exposure must be evident
- 2- The patient must demonstrate signs and symptoms typical of the metal (toxic)
- 3- Abnormal metal concentration in the appropriate tissue must be evident

Note: if one of these features is absent, one cannot make a conclusive diagnosis of metal toxicity

DIAGNOSING TOXICITY

- In clinical practice, analysis of toxic elements should always be considered in the clinical workup of the patient with :
- 1- Renal disease of unexplained origin
- 2- Bilateral peripheral neuropathy
- 3- Acute changes in mental function
- 4- Acute inflammation of the nasal or laryngeal epithelium
- 5- A history of exposure
- The laboratory plays a key role in this process, and appropriate specimen collection coupled with accurate analysis will make a major difference in correct diagnosis.

ROUTES OF EXPOSURE

- Toxins can enter the body via several routes :
- Ingestion, inhalation, and transdermal absorption are the most common.
- For most toxins to exert a systemic effect, they must be absorbed into circulation.
- Some are taken up by processes intended for dietary nutrients. However, most are absorbed by passive diffusion.
- This process requires that the substance cross cellular barriers.
- Hydrophobic substances have the ability to diffuse across cell membranes and therefore , can be absorbed anywhere along the gastrointestinal tract.
- Ionized substances cannot passively diffuse across membranes.

- Other factors can influence the absorbance of toxins from gastrointestinal tract including;
- Rate of dissolution
- Gastrointestinal motility
- Resistance to degradation in the gastrointestinal tract
- Interaction with other substances
- Toxins that are not absorbed from the gastrointestinal tract do not produce systemic effects but may produce local effect, such as diarrhea, bleeding, or malabsorption of nutrients, which may cause systemic effects secondary to toxin exposure

ACUTE AND CHRONIC TOXICITY

- They are terms used to relate the duration and frequency of exposure to observed toxic effects
- **Acute toxicity :** Is usually associated with a single, short-term exposure to a substance, the dose of which is sufficient to cause immediate toxic effect.
- **Chronic toxicity:** Is usually associated with repeated frequent exposure for extended periods, at doses that are insufficient to cause an immediate acute response.

SPECIFIC METALS

- The Agency for toxic substances and disease registry (ATSDR): produces “ toxicological profile” for many of the toxic metals .
- The hazardous substances are ranked based on their frequency of occurrence, toxicity, and potential for human exposure.
- Several of these metals are considered essential trace elements.

ARSENIC (AS)

- Is widely known to be a toxin having gained notoriety from its extensive use by Renaissance nobility as anti syphilitic agent and an antidote against arsenic poisoning “ because chronic administration of low doses protect against acute poisoning by massive doses “
- Serum concentrations of arsenic are elevated for only a short time after administration, after which arsenic rapidly disappears into the large body phosphate pool.
- After ingestion, abnormal serum arsenic concentrations are detected for less than 4 hrs.

TOXICITY OF AS

- Arsenic binds to dihydrolipoic acid, a necessary cofactor for pyruvate dehydrogenase. Absence of the cofactor inhibits the conversion of pyruvate to acetyl coenzyme a, the first step in Citric acid cycle .
- Arsenic competes with phosphate for reaction with adenosine diphosphate (ADP), resulting in formation of a lower energy ADP rather than ATP.
- Arsenic binds with any hydrated sulfhydryl group on protein, distorting the 3-dimentional configuration of protein and thus causing it to lose activity.
- Arsenic is known to interfere with the activity of several enzymes of heme biosynthetic pathway.
- There is evidence of an increased risk of bladder, skin, and lung cancer following consumption of water with high arsenic contamination.

TOXICITY OF AS

- British antilewisite (BAL) is an effective antidote for treating arsenic intoxication, the active agent is dimercaprol, a sulfhydryl- reducing agent.
- hair analysis is frequently used to document time of arsenic exposure. When As circulation in blood will bind to protein by formation of a covalent complex with sulfhydryl groups of the amino acid cysteine.
- Because arsenic has a high affinity for keratin, which has high cysteine content, the As concentration in hair or nails is higher than in other tissue.

COPPER

- Cu ingestion has been found to lead to serious toxicity, and it may be encountered as pesticide.
- Cu is one of the active agents in marine antifouling paints and as a wood preservative.
- Ingestion of these sources induce:
- 1-Severe gastrointestinal upset with severe irritation of the epithelial layer of the GIT.
- 2- Hemolytic anemia.
- 3- Centrilobular hepatitis with jaundice.
- 4- Renal damage.
- 5- Excess Cu ingestion interferes with absorption of Zn that leads to Zn deficiency.
- 6- The classic presentation of Cu toxicosis is represented by the genetic disease of Cu accumulation known as Wilson disease (hepatocellular damage)

IRON

- Iron supplements are used frequently to maintain an adequate body burden of iron.
- Ingestion exceeds the needed daily requirement, resulting in iron toxicity.
- Acute ingestion of more than 0.5 gm of iron has been observed to produce severe irritation of the epithelial lining of GIT and result in hemosiderosis, which may develop into hepatic cirrhosis.
- The presence of excessive amounts of iron in serum & urine defines this diagnosis.

LEAD

- Lead is a metal commonly found in the environment.
- It is considered both acute & chronic toxin.
- Pb present at high concentration in many paint manufactured .
- Ceramic products for use in home, such as dishes or bowls, has been found to contain significant amount of Pb.
- Pb is found in dirt from areas adjacent to homes painted with lead-based paints & on highways where it has accumulated from the use of leaded gasoline in automobiles.
- Pb is found in soil near abandoned industrial sites were lead may been used.
- Water transported through lead or lead-soldered pipe contains Pb.

LEAD TOXICITY

- The fraction of lead absorbed is enhanced by nutritional deficiency . The majority excreted in the stool.
- Significant fraction of the absorbed is rapidly incorporated into bone & erythrocytes, & ultimately distributed among all tissues.
- Lipid-dense tissue, such as the central nervous system, are particularly sensitive to organic forms (tetra-methyl lead) .
- All lead absorbed is excreted in bile or urine.
- Soft tissue turnover of lead occurs within 120 days.

LEAD TOXICITY

- Lead expresses its toxicity by several mechanisms:
- It inhibits aminolevulinic acid dehydratase (ALAD) , one of the enzymes that catalyze synthesis of heme .
- Anemia caused by lack of heme is frequently observed .
- Lead is an electrophile that forms covalent bonds with sulfhydryl group of cysteine in proteins. thus, proteins in all tissue exposed to lead.
- Keratin in hair contains a high fraction of cysteine and avidly binds to lead.
- Hair analysis for lead is good marker for exposure.
- Children are prone to the effect of lead because they have greater opportunity for exposure.
- The test for lead toxicity is measurement of the concentration of blood lead.

THALLIUM

- Thallium (Tl) is a byproduct of lead smelting.
- Thallium is found in high concentration in rodenticide.
- It is a waste product of coal combustion and the manufacturing of cement.
- Thallium is rapidly absorbed via ingestion, inhalation, and skin contact.
- The mechanisms of toxicity are:
- 1-Competition with potassium at cell receptors to affect ion pumps.
- 2-Inhibition of DNA synthesis
- 3- Binding to sulfhydryl groups on proteins in neural axons.
- 4- Concentration in renal tubular cells to cause necrosis
- Patients who exposed to thallium demonstrate alopecia, peripheral neuropathy, seizures, & renal failure
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MERCURY (HG)

- The atmosphere and surface of the earth are exposed to several thousand tons of Hg.
- 1-As a result of the natural outgassing of rock (30,000 ton/yr)
- 2- From industry where it is used in electrolysis, in electrical switches, & fungicide.
- 3- From its incorporation into dental amalgams (90 ton/yr).
- 4- Used extensively in the pulp and paper s a whitener.

MERCURY TOXICITY

- Mercury is essentially nontoxic in its elemental form.
- In the absence of any chemical or biological system that chemically alters Hg.
- It is possible to consume it orally without any significant side effect.
- However, once Hg is chemically modified to the ionized inorganic species (Hg+2), it becomes toxic.
- In adults, cases of methylmercury poisoning are characterized by focal degeneration of neurons in regions of the brain, such as the cerebral cortex and cerebellum.
- Analysis of blood, urine, and hair for mercury concentration is used to determine exposure.

MERCURY TOXICITY

- Mercury toxicity is expressed in 3 ways :
- 1- Hg+2 reacts with sulfhydryl groups of protein, causing change in the tertiary structure of the protein with the loss of the biological activity associated with that protein. Because it becomes concentrated in kidney during clearing process, the kidney is the target organ that experience the greatest toxicity.
- 2- With the tertiary change, some proteins become immunogenic, eliciting a proliferation of B-lymphocytes that generate immunoglobulins to bind the new Ag.
- 3- Alkyl Hg species, such as methylmercury, are lipophilic and binds to proteins in lipid-rich tissue, such as neurons, myelin in particular.

ANALYTICAL METHODS

- **Metals is measured in biological fluids with number of analytical techniques including:**
- **1- Atomic absorption spectrometry with flame. (AAS-F)**
- **2- Inductively coupled plasma-optical emission spectrometry. (ICP-OES)**
- **3- Inductively coupled plasma-mass spectrometry. (ICP-MS)**
- **4- High-performance liquid chromatography-mass spectrometry (LC-MS)**


Thank You