COMBINED DAMAGE TO THE NERVOUS SYSTEM AND LIVER AS A RESULT OF ARSENIC POISONING AND CHANGES IN BIOCHEMICAL PARAMETERS IN THE BLOOD OF EXPERIMENTAL ANIMALS

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Abstract
Arsenic is regarded as a group I carcinogen for humans . The major cause of human arsenic toxicity is from contamination of drinking water from natural geological sources rather than from mining, smelting and agricultural sources (pesticides or fertilizers) . Arsenic contamination in the ground water has been reported worldwide . Studies on populations from different parts of the world exposed to comparable levels of arsenic in drinking water show varying degrees of individual susceptibility to arsenic-induced genetic damage, metabolism, methylation capacity and other health effects . Also, within the same population exposed to arsenic only a minor percentage actually develop arsenic-induced skin lesions that are considered to be the hallmark of arsenicosis. Research We conducted experiments on 15 white rats weighing 140-260 g, kept in the vivarium under normal conditions at the Scientific Research Center of the Azerbaijan Medical University, and divided them into 3 groups. The concentrations of the enzymes alanine amino transferase (ALT), aspartate amino transferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), and creatine phosphokinase (CPK) were determined in the blood of experimental animals.

Keywords: arsenic poisoning, experimental animals, nervous system, liver

Introduction

Consequently, it is of utmost importance to understand the underlying molecular mechanisms that render a person susceptible to arsenic toxicity. Substantial scientific progress has been made recently in the area of arsenic metabolism, pharmacokinetics, modes of carcinogenic action and in different model systems including human cell line [1].

Single doses of inorganic arsenic may be highly toxic by ingestion and inhalation. Ingestion of large doses of arsenic can rapidly lead to GI disturbance, encephalopathy, and potentially peripheral neuropathies. In severe poisonings, multi-organ features will develop within hours, these include rhabdomyolysis, renal failure, respiratory failure, failure of vital cardiovascular and brain functions and death. The fatal dose for inorganic arsenic ingestion in humans is often quoted as 1 to 3mg/kg, though survival at higher doses has been observed. Chronic exposure to inorganic arsenic has been extensively studied in areas of the world with naturally high levels. Chronic arsenic exposure may result in a wide range of signs and symptoms, many non-specific [2,3,4]. Skin lesions including palmoplantar hyperkerotosis, hyperkaratinized warts or corns and hyper pigmentation (interspersed with areas of depigmentation) are thought to be the most sensitive indicator of chronic exposure to high levels [5,6].

Among the various internal organs affected by chronic exposure to arsenic in humans, liver is one of the important targets. Epidemiological studies have shown association between chronic arsenic exposure and liver disease including hepatomegaly, hepatoportal sclerosis, liver fibrosis and cirrhosis of liver . Abnormal liver functions as manifested by severe gastrointestinal problems and clinical elevations of liver enzymes in plasma including alanine amino transferase (ALT), asparatate amino transferase (AST), alkaline phosphatase (ALP) also are associated with chronic arsenic exposure . Exposure of mice to arsenic in drinking water causes elevation of liver enzymes in plasma and capilarization of liver sinusoidal endothelium . Infact, liver is the major site of arsenic metabolism and hence arsenic exposure causes liver disease in exposed humans [7,8,9].

Antinuclear antibodies (ANA) are a diverse group of autoantibodies that are found in autoimmune disorders like systemic lupus erythomatosus, Rheumatoid arthritis, Sjorgen's syndrome, systemic sclerosis and inflammatory myositis. Arsenic exposure increases the incidence of auto-immune diseases like diabetes mellitus . ANA are present in lower titers in liver diseases, leprosy, multiple sclerosis and juvenile rheumatoid arthritis .The association of chronic arsenic exposure and autoimmune disorders has received only minimal attention [10,11,12].

Material and methods

Research We conducted experiments on 15 white rats weighing 140-260 g, kept in the vivarium under normal conditions at the Scientific Research Center of the Azerbaijan Medical University, and divided them into 3 groups.

While conducting experiments, the rules of behavior with experimental animals of the European Bioethical Commission (Strasbourg 1986) and the local bioethical commission of the Azerbaijan Medical University were strictly followed. n all cases, the experiments were performed under anesthesia conditions, and at the end of the experiment, anesthesia was created by injecting 0.5 ml of calypsol solution into their abdominal cavity. The white rats selected for the experiment were divided into 3 groups with 5 heads in each.

Group 1 included intact rats.

Creation of a pathological model in rats as a result of poisoning with arsenic-contaminated water in group 2.

Changes in biochemical indicators of liver enzymes in the blood of white rats in group 3 were studied 10 days after the cessation of poisoning.

The concentrations of the enzymes alanine amino transferase (ALT), aspartate amino transferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), and creatine phosphokinase (CPK) were determined in the blood of experimental animals [13,14,15].

Results and discussion.

The concentration of AST enzyme in the blood of experimental animals included in group 1 varied between 25-33 u/l, ALT enzyme concentration 30-40 u/l, glutamine transferase enzyme concentration 28-58 u/l, lactate dehydrogenase (LDH) enzyme concentration 270-440 u/l, creatine phosphokinase (CPK) enzyme concentration 243-275 u/l, and alkaline phosphatase (ALP) enzyme concentration 150-300 u/l.

Based on the results obtained from experimental animals, it was determined that the average concentration of the AST enzyme in the blood of intact white rats was 29,4±1,50 u/l (σ=3.36), the average concentration of the ALT enzyme was 35,2±1,85 u/l, (σ=4,15), the average concentration of the glutamine transferase enzyme was 43,2±5,43 u/l (σ=12,13), the average concentration of the LDH enzyme was 368±28,53 u/l (σ=63,80), the average concentration of the CPK enzyme was 260,4±6.00 u/l (σ=13,41), and the average concentration of the alkaline phosphatase enzyme was 234±27,13 u/l (σ=60,66).

In group 2, the average concentration of glutamine transferase enzyme increased by 26% compared to the intact state, and the average concentration of LDH enzyme increased by 21%, reaching 54,6±3.01 (σ=6,73) and 386±9,27 u/l (σ=20,74), respectively.

The average concentration of CPK enzyme increased by 6% compared to the intact state, reaching 277±13,73 u/l (σ=30,70), and the average amount of alkaline phosphatase enzyme increased by 18%, reaching 276,4±21,32 u/l (σ=47,67).

In the blood taken from the hepatic vein of the experimental animals in group 3, the concentration of the AST enzyme was recorded between 30-62 u/l, the concentration of the ALT enzyme was 42-55 u/l, the concentration of the glutamine transferase enzyme was 42-65 u/l, the concentration of the LDH enzyme was 360-400 u/l, the concentration of the CPK enzyme was 266-346 u/l, and the concentration of the alkaline phosphatase enzyme was 230-360 u/l. Their average concentration was also significantly reduced compared to group 2.

In the blood taken from animals of group 3, the average concentration of ALT and AST enzymes decreased by 5%, to 36,2±2,13 u/l (σ=4,76) and 47,2±2,35 u/l (σ=5,26), respectively. The average concentration of glutamine transferase enzyme decreased by 6%, to 51,4±4.01 u/l (σ=8,96), the average concentration of LDH enzyme decreased by 2%, to 379±7,48 u/l (σ=16,73), the average concentration of CPK enzyme decreased by 295,2±13,61 u/l (σ=30,43), and the average concentration of alkaline phosphatase enzyme decreased by 2%, to 271,2±23,74 u/l.

The average concentration of AST, ALT, and glutamine transferase enzymes decreased significantly by two times compared to group 2, while the concentration of other enzymes decreased slightly. However, despite this positive change, the average concentrations of the remaining enzymes, except for the LDH enzyme, were significantly higher compared to the intact state. The average concentration of the AST enzyme increased by 23% ($p<0.05$), the average concentration of the ALT enzyme by 34% ($p<0.01$), the average concentration of the glutamine transferase enzyme by 19%, the average concentration of the LDH enzyme by 3%, the average concentration of the CPK enzyme by 13% ($p<0.05$), and the average concentration of the alkaline phosphatase enzyme by 16%. The accuracy of the difference according to intact indicators was inaccurate for the enzymes glutamine transferase, LDH, and alkaline phosphatase [16,17,18].

Conclusions

The results of our experiments show that as a result of arsenic poisoning, the concentration of enzymes synthesized in the liver, including aspartate and alanine transferase, glutamyl transferase, lactate dehydrogenase, creatine phosphokinase, and alkaline phosphatase, increases in blood taken from the portal vein of the liver [19,20].

References:

1. Riaz MA, Nisa ZU, Anjum MS, et al. Assessment of metals induced histopathological and gene expression changes in different organs of non-diabetic and diabetic rats. Sci Rep 2020; 10: 1–11. doi: 10.1038/s41598-019-56847-4.

2. Carmean CM, Yokoi N, Takahashi H, et al. Arsenic modifies serotonin metabolism through glucuronidation in pancreatic β-cells. Am J Physiol Endocrinol Metab. 2019; 316(3): E464–E474. doi: 10.1152/ajpendo.00302.2018.

3. Wang M, Hossain F, Sulaiman R, et al. Exposure to inorganic arsenic and lead and autism spectrum disorder in children: a systematic review and meta-analysis. Chem Res Toxicol 2019; 32(10): 1904–1919. doi: 10.1021/acs.chemrestox.9b00134.

4. Bozack AK, Saxena R, Gamble M V. Nutritional influences on one-carbon metabolism: effects on arsenic methylation and toxicity. Annu Rev Nutr 2018; 38: 401–429. doi: 10.1146/annurev-nutr-082117-051757.

5. Jain N, Chandramani S. Arsenic poisoning-an overview. Indian J Med Spec 2018; 9: 143–145.

6. Goel A, Ramakrishna B, Zachariah U, et al. What makes non-cirrhotic portal hypertension a common disease in India? analysis for environmental factors. Indian J Med Res. 2019; 149(4): 468–478. doi: 10.4103/ijmr.IJMR_1405_17.

7. Hsu LI, Wang YH, Hsieh FI, et al. Effects of arsenic in drinking water on risk of hepatitis or cirrhosis in persons with and without chronic viral hepatitis. Clin Gastroenterol Hepatol 2016; 14: 1347–1355. doi: 10.1016/j.cgh.2016.03.043.

8. Li X, Sun D, Zhao T, et al. Long non-coding RNA ROR confers arsenic trioxide resistance to HepG2 cells by inhibiting p53 expression. Eur J Pharmacol 2020; 872: 172982. doi: 10.1016/j.ejphar.2020.172982.

9. Dugo EB, Yedjou CG, Stevens JJ, et al. Therapeutic potential of arsenic trioxide (ATO) in treatment of hepatocellular carcinoma: role of oxidative stress in ATO-induced apoptosis. Ann Clin Pathol. 2017; 5(1). 2017;5(1):1101. Epub 2017 Jan 4.

10. Sadaf N, Kumar N, Ali M, et al. Arsenic trioxide induces apoptosis and inhibits the growth of human liver cancer cells. Life Sci 2018; 205: 9–17. doi: 10.1016/j.lfs.2018.05.006

11. Grau-Pérez M, Kuo CC, Spratlen M, et al. The association of arsenic exposure and metabolism with type 1 and type 2 diabetes in youth: the search case-control study. Diabetes Care 2017; 40: 46–53. doi: 10.2337/dc16-0810.

12. Rehman K, Fatima F, Akash MSH. Biochemical investigation of association of arsenic exposure with risk factors of diabetes mellitus in Pakistani population and its validation in animal model. Environ Monit Assess 2019; 191(8): 511. doi: 10.1007/s10661-019-7670-2.

13. Manthari RK, Tikka C, Ommati MM, et al. Arsenic induces autophagy in developmental mouse cerebral cortex and hippocampus by inhibiting PI3K/Akt/mTOR signaling pathway: involvement of blood–brain barrier's tight junction proteins. Arch Toxicol 2018; 92(11): 3255–3275. doi: 10.1007/s00204-018-2304-y.

14. Cardenas A, Smit E, Welch BM, et al. Cross sectional association of arsenic and seroprevalence of hepatitis B infection in the United States (NHANES 2003–2014). Environ Res 2018; 166: 570–576. doi: 10.1016/j.envres.2018.06.023.

15. Alex AA, Ganesan S, Palani HK, et al. Arsenic trioxide enhances the NK cell cytotoxicity against acute promyelocytic leukemia while simultaneously inhibiting its bio-genesis. Front Immunol 2018; 9: 1–13. doi: 10.3389/fimmu.2018.00001.

16. Suntararuks S, Worasuttayangkurn L, Akanimanee J, et al. Sodium arsenite exposure impairs B cell proliferation and enhances vascular inflammation in plasmodium berghei mouse model. Environ Toxicol Pharmacol 2019; 66: 7–13. doi: 10.1016/j.etap.2018.12.010.

17. Veenema R, Casin KM, Sinha P, et al. Inorganic arsenic exposure induces sex-disparate effects and exacerbates ischemia-reperfusion injury in the female heart. Am J Physiol Hear Circ Physiol 2019; 316(5): H1053–H1064. doi: 10.1152/ajpheart.00364.2018.

18. Seow WJ, Pan WC, Kile ML, et al. Arsenic reduction in drinking water and improvement in skin lesions: a follow-up study in Bangladesh. Environ Health Perspect 2012; 120(12): 1733–1738. doi: 10.1289/ehp.1205381

19. Al-Eryani L, Jenkins SF, States VA, et al. MiRNA expression profiles of premalignant and malignant arsenic-induced skin lesions. PLoS One 2018; 13(8): e0202579. doi: 10.1371/journal.pone.0202579.

20. Weinmuellner R, Kryeziu K, Zbiral B, et al. Long-term exposure of immortalized keratinocytes to arsenic induces EMT, impairs differentiation in organotypic skin models and mimics aspects of human skin derangements. Arch Toxicol 2018; 92: 181–194. doi: 10.1007/s00204-017-2034-6.