

Review

Poisonings with heavy metals and neoplasms - possible correlations

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As a side effect of industrialization, some diseases have developed only recently, becoming a challenge for the medical specialists both in research and medical treatment fields. Among these, the poisoning with heavy metals occupies a certain category that must retain attention, due to since the effects of this kind of poisoning are very serious effects if these injuries poisonings are not properly recognized and treated. Most common heavy metals that are involved in poisonings are Mercury, Cadmium, Lead and Arsenic. They are capable of inducing a wide range of pathologies, including neoplasms with cerebral localization. In order to illustrate the link between the poisonings with heavy metals and neoplasms, we present a case of a 19 years old patient, who was diagnosed both with germinoma, which is a malignant tumor of the median brain structures, and mercury poisoning. Since germinoma and mercury poisoning are rare conditions, it is very hard to obtain enough data for a statistically significant study. However, the case study which encompasses the poisoning with heavy metals and germinoma supports the idea of performing proper screenings in the event of individuals being diagnosed with mercury poisoning, especially when they can turn out to be potentially treatable.

Key words: Poisoning, mercury poisoning, germinoma, cerebral tumor, cerebral neoplasm.

INTRODUCTION

Along with the widespread of industrialization and urbanization, the contamination with heavy metals has become a major environmental issue, which affects the metabolism of organisms in ecosystems, because of its toxic character, as well as its high prevalence and persistence (Järup, 2003; He et al., 2013). Generally, the metals whose density is $> 5 \text{ g / cm}^3$ are considered heavy

metals. Among them, Pb, Cd, Hg, Cr and As usually exist in the environment but are considered to be the primary toxic heavy metals for human health (Yuan et al., 2016).

Environmental contamination and exposure to heavy metals is a serious issue all over the world. Its impact dramatically increased in the last 50 years as a result of the exponential increase in the use of heavy metals in

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industrial processes and products. Some metals are found naturally in our bodies and are essential to human health, being necessary for a normal metabolism (eg. Cu, Zn, Mn, Co) however, they become toxic in high concentrations. Other elements, such as Hg, Cd, As, Ni and Pb are extremely toxic and can have devastating effects even in very low concentrations. They have the tendency to accumulate both in the food chain and in the human body, namely in the soft tissues (kidneys, liver, brain) as well as in the hard tissues (bones), being actually systemic toxins with specific neurotoxic, nephrotoxic and teratogenic effects (Alloway, 1995; Huang et al., 2008; Kabata-Pendias and Mukherjee, 2007). Moreover, heavy metals can alter a long line of metabolic processes, including the endocrine system. In the last decade, studies on heavy metals that potentially interact with the endocrine system have increased significantly, emphasizing that they are disruptive for the endocrine system (Rodríguez et al., 2007). Among their various mechanisms of action, these metals are capable of exerting an estrogenic activity upon humans and animals. Choe and Coll. (2003) have found a high estrogenicity in Cd, followed by Co, Pb, Cr and Cu; these metals being considered as a new class of environmental non-steroidal estrogen. Martin and Coll. discovered reported that Co, Cu, Ni, Pb, Hg or Cr, reduced the concentration of receptor estrogen protein and an induced expression of the estrogen genes, which regulate the progesterone receptor, was noticed (Martin et al., 2003).

Some studies have shown that exposure to heavy metals is damaging to the nervous, hematological and cardiovascular systems, increases the risk of various types of cancer, such as kidney, lungs, liver, skin and gastric cancers (Järup, 2003; He et al., 2013; Welling et al., 2015). Some metals, such as Cr, Pb, As, Cd and Hg, have been classified as specific or probable cancer agents by the International Agency of Cancer Research (Järup, 2003; Welling et al., 2015). In the same vein, many researchers declared that the exposure to heavy metals has increased the incidence and mortality in the case of gastric cancer. The Cr concentration of soil is correlated with mortality of women who have upper gastro-intestinal cancer (GI). Long term exposure to low levels of As and Cr in the plant soil may be a potential risk factor in the appearance of cancer (Núñez et al., 2016). Between 2005 and 2010, the levels of As in the soil were significantly correlated with the rate of mortality by gastric, colon, kidney nose-pharynx and lungs cancer. Similarly, long term exposure to Cd and Pb has increased the mortality risk of many types of cancer, including pulmonary, esophagus and gastric cancers (Yuan et al., 2016).

Among all heavy metals, Cd, Hg, Pb and As are some of the most toxic elements because of their persistence in The environment. They produce oxidative, nitrosative

stress and the deterioration macromolecules in the cells, which, in turn, lead to the death of cells by apoptosis or necrosis. Although the toxicity of heavy metals upon the organisms has serious ecological consequences, the metals rarely appear in isolation, more in mixtures. As such, metallic mixtures substantially complicate the process of risk assessment for these elements and very few researchers studied the impact of heavy metal mixtures upon the environment. Little information is available on the potential side effects upon health, related to the administration of contaminants containing a mixture of the most frequently met heavy metals. Therefore, it is a must to study heavy metals not only individually, but also in mixtures. Metallic metabolism has significant effects upon the toxicity of metals. The protection processes at molecular and cellular levels cannot have an impact upon cellular homeostasis even after the exposure to the metal. One example that has been studied and it is known to alter sensitivity to metals is glutathione (GSH). GSH can interfere with toxic metals by modifying the absorption rate and elimination of metals and can protect against oxidative stress resulted from the redox reactions catalyzed by the metal (Egiebor et al., 2013).

Heavy metals, such as methylmercury (MeHg), are environmental pollutants that easily affect humans by bio-accumulation through the food chain. Several reports uphold the idea that the Central Nervous System represents a major target of mercury and the endocrine organs can accumulate large concentrations of it. Studies carried out on humans have proved that individuals exposed to various forms of mercury show a significant concentration of mercury in their hypophysis gland (Pinheiro et al., 2007; Crespo-Lopez et al., 2007; Oliveira et al., 2006; Falnoga et al., 2000).

The pituitary gland is a critical neural-endocrine organ, with posterior attachment to the hypothalamus. The front lobe (or adenohypophysis) of the hypophysis is anatomically different from the hypothalamus and contains a collection of endocrine cells. The secretory cells of the adenohypophysis include somatotrophs (almost 50%), which produce somatotropin (a growth hormone, GH); Corticotropic hormones (15 to 20%), which release the adrenocorticotrophic hormone; Gonadotrophs (10 to 15%), which synthesize the luteinizing hormone and the hormone of follicular stimulation; Thyrotrophs (3 to 5%), which release the hormone of thyroid stimulation; and, finally lactotrophs (10 to 25%), which release prolactin (PRL). The issues in hypophysis physiology result in the hypo- or hyper secretion of these hormones. Although the pituitary gland has already been pointed out as a potential target of mercury accumulation, the impact of this metal upon the regulation of hormone release is unclear. Previous studies have shown (both positive and negative) associations between serum exposure to PRL and exposure to

mercury. This dual effect can be explained by different interactions between the types of mercury (inorganic and organic) and the secretion of PRL by the pituitary gland, which is controlled by neural-transmitters, such as dopamine. Thus, it has been suggested that serum PRL can be a possible biomarker of exposure to heavy metals (Maues et al., 2015).

Germinomas are a distinctive category of heterogenic tumors that are prone to be developed in the structures of cerebral medial line, most frequent localization being in the pineal gland or the neuro-hypophyseal region (Shankar et al., 2016). It is a very rare type of neoplasm, which account for less than 1% of the total intracranial cancers. However, it is more frequent in children, representing between 3 and 8% of the pediatric and adolescent neoplasms. The highest incidence of diagnosis is in the age interval between 10 and 21 years. The incidence is higher in Asia than in Western Europe and United States of America. It appears more often in males than in females. The 5-year survival rate is between 70 and 90% of the patients (Pluschke, 2013). From a histologic perspective, germinomas are tumors similar to dysgerminomas and seminomas, which are germinal tumors; the provenience of these tumors being in germinal cells that do not migrate properly during the intrauterine life. Certain causes that lead to the development of germinomas and/or the transformation of the cells of the germinoma from a premalignant to a malignant stage have not yet been identified. But the causes suspected to be involved in this process, include the poisoning with heavy metals (Vasiljevic et al., 2015).

First signs that raise the suspicion of a germinoma and lead the patient to present to a medical unity are nonspecific and usual for almost any type of intracranial growth. Headaches, dizziness and vomiting without any other cause are among those symptoms. Other sign of a germinoma may be the development of hydrocephaly. The possibility of a germinoma diagnostic is indicated by the imagistic investigations, which reveal a tumoral mass in a specific localization. Other related diseases are hypopituitarism, visual field deficits (especially when looking upwards) and diabetes insipidus. Some of these morbidities may persist regardless of administered treatment (Shankar et al., 2016; Vasiljevic et al., 2015).

The diagnosis is based on imagistic, morphologic and biochemical criteria. From the imagistic perspective, the most useful investigation is the MRI, which provides useful information regarding the localization of the tumor, the dimensions, shape and any other vicinity structures that might be affected (Reddy et al., 2015). The diagnostic dilemma in the case of a germinoma is whether to perform a biopsy or not. The certain diagnostic is evidently based on a biopsy with the histopathological examination of the biopsy sample. The evolution of germinomas is usually favorable with a treatment consisting of an association between chemotherapy and

radiotherapy, with a full recovery expectance in the majority of cases. On the other hand, due to the deep localization of this type of tumor in the brain, a biopsy can trigger a series of complications which make some experts and medical practitioners to consider it highly risky (Awa et al., 2014). Adding the fact that the patients are typically children and teenagers at whom is expected a full recovery after a proper treatment, the risk of impairment due to cerebral biopsy exceeds the benefits of having a histopathological confirmed diagnosis of germinomas, especially in the suspected cases that fit the profile of a young male. In this case, often the therapeutic decision is to start the treatment without a morphologic confirmation of the diagnosis (Awa et al., 2014).

Germinomas localized in the pineal region produce elevated level of beta-human chorionic gonadotropic (HCG), alfa fetal protein (AFP) and carcinoembryonic antigen (CAE). The determination of high levels of these substances in the blood stream and cerebrospinal fluid is an argument in the diagnosis process and can serve as a further argument for not performing a cerebral biopsy (Ogino et al., 2005)

Treatment of germinomas consists of an association between chemotherapy, radiotherapy and/or surgery. Surgery is useful when possible, despite the fact that it does not remove entirely the tumor, but it helps in reducing its dimensions, and by this, the risk of local mechanic complication, such as hydrocephaly, is diminished. However there are certain complications, particularly in the cases in which the tumor is located very deep. By operating deep on the brain, certain damage can be produced, that sometimes, exceeds the benefits of the surgery. On the other hand, there is a continuous concern for developing new and less invasive neurosurgical techniques for tumors located in less accessible parts. Hydrocephaly itself can beneficiate from surgical approach, such as the ventricular drain placement. Chemotherapy is very useful in the treatment of germinomas because the cells are sensible to it. Radiotherapy in association with chemotherapy is indicated whenever there are no contraindications regarding this kind of therapy (Packer et al., 2000).

CASE REPORT

To illustrate the hypothesis that heavy metal poisoning, in particular, mercury poisoning, might be involved in the development and aggravated evolution of a germinoma, we present the case of a 19-years old Romanian patient, from a rural region. This patient did not have significant previous pathologies, neither did the medical history of her family revealed anything of importance for the current developed pathology.

This patient was admitted in a neurosurgery hospital

from an academic city with symptoms including headaches and impaired vision. An MRI was performed and the results showed an irregular growth in the pineal region and imagistic signs of hydrocephaly. After this, she left voluntarily the hospital, only to return a few days later, presenting the same symptoms. The preferred therapeutic treatment was towards a neurosurgical procedure of placement of a ventricular drain in order to cure the symptoms of hydrocephaly, although it was secondary to a tumoral mass of unknown etiology in the pineal region.

Two weeks after the surgery, the patient returned with violent headaches. A new MRI was performed and revealed that both the tumor from the pineal region and the hydrocephaly have increased in size. A new neurosurgical procedure consisting of the replacement of the ventricular drain was performed, with improved symptomatology in the postsurgical interval. Beta-HCG and AFP biomarkers were also determined and the values were within normal ranges. Based on neuro-imagistic criteria, the patient was diagnosed with germinoma. Another important determination performed during this admittance was the determination of urinal mercury in urine, which had a value of 165 µg%, well above normal values of between 0.2 to 13 µg%.

Further investigations could not be performed, because of the rapid progression of the disease. On the last hospitalization, the patient had signs of cranial nerve damage, along with multiple cerebral periventricular masses which were interpreted as secondary determinations with the origin in the primary tumoral site from the pineal region. The evolution was unfavorable, resulting in the death of the patient.

CONCLUSION

Based on the current stage of knowledge about the intoxications with heavy metals, which were demonstrated to be capable of inducing neoplasms, and germinomas, which have not had the mechanism of occurrence determined beyond doubt, we find the presentation of the case study above useful in providing further information for both domains of interest, namely research and medical treatment.

Due to the possible link between poisoning with heavy metals and the development of germinoma, we believe it is useful to conduct screening both on patients with poisoning with heavy metals and patients with germinoma, as well as on other patients with different types of cerebral malignant tumors. We think this is particularly useful, as both poisonings and some of the cerebral tumors, if early diagnosed, can benefit from proper, adequate treatment in order to prevent mortality, morbidity, and sometimes even achieve a complete recovery.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

ABBREVIATIONS

AFP, alfa fetal protein; **As**, arsenic; **CAE**, carcinoembryonic antigen; **Cd**, cadmium; **Co**, cobalt; **Cu**, copper; **GH**, growth hormone; **GSH**, glutathione; **HCG**, human chorionic gonadotropic; **Hg**, mercury; **MeHg**, methyl mercury; **Mn**, manganese; **MRI**, magnetic resonance imaging; **Ni**, nickel **Pb**, plumb lead; **PRL**, prolactin; **Zn**, zinc.

REFERENCES

- Alloway BJ (1995). Soil processes and the behaviour of heavy metals, Heavy metals in soils pp. 7-28.
- Awa R, Campos F, Kazunori A, Kazuhiko S, Atsushi T, Kaoru K, Fumiyuki Y, Prasanna K, Hiroshi T, Yoshihiko F, Yukihiko F, Ryosuke H, Tatsuki O (2014). Hirofumi H. Neuroimaging diagnosis of pineal region tumors-quest for pathognomonic finding of germinoma. *Neuroradiology* 56:525-534.
- Crespo-Lopez ME, Lima de SA, Herculano AM, Rodriguez BR, Martins do Nascimento JL (2007). Methylmercury genotoxicity: a novel effect in human cell lines of the central nervous system. *Environment International* 33:141-146.
- Egiebor E, Tulu A, Abound YN, Aighewi IT, Ishaque A (2013). The kinetic signature of toxicity of four heavy metals and their mixtures on MCF7 breast cancer cell line. *International Journal of Environmental Research and Public Health* 10:5209-5220.
- Falnoga I, Tusek ZM, Horvat M, Stegnar P (2000). Mercury, selenium, and cadmium in human autopsy samples from Idrja residents and mercury mine workers. *Environmental Research* 84:211-218
- He B, Yun Z, Shi J, Jiang G (2013). Research progress of heavy metal pollution in China: sources, analytical methods, status, and toxicity. *Chinese Science Bulletin* 58(2):134-140.
- Huang M, Zhou S, Sun B, Zhao Q (2008). Heavy metals in wheat grain: Assessment of potential health risk for inhabitants in Kunshan, China *Science of the Total Environment* 405:54-61.
- Järup L (2003). Hazards of heavy metal contamination. *British Medical Bulletin* 68:167-182.
- Kabata-Pendias A, Mukherjee AB (2007). Trace elements from soil to human, Springer-Verlag Berlin Heidelberg pp. 84-90.
- Martin MB, Reiter R, Pham T, Avellanet YR, Camara J, Lahm M, Pentecost E, Pratap K, Gilmore BA, Divekar S, Dagata RS, Bull JL, Stoica A (2003). Estrogen-like activity of metals in MCF-7 breast cancer cells. *Endocrinology* 144(6):2425-2436
- Maues L, Crespo-Lopey ME, Nasciutti LE, Picanco-Diniz D, Antunes-Rodrigues J, Braz J (2015). Methylmercury inhibits prolactin release in a cell line of pituitary origin. *Medical and Biological Research* 48(8):691-696.
- Núñez O, Fernández-Navarro P, Martín-Méndez I, Bel-Lan A, Locutura JF, López-Abente G (2016). Arsenic and chromium topsoil levels and cancer mortality in Spain. *Environmental Science and Pollution Research* 23(17):17664-17675.
- Ogino H, Shibamoto Y, Takanaka T, Suzuki K, Ishihara S, Yamada T, Sugie C, Nomoto Y, Mimura M (2005). CNS germinoma with elevated serum human chorionic gonadotropin level: clinical characteristics and treatment outcome *International Journal of Radiation Oncology, Biology, Physics* 62(3):803-808
- Oliveira FR, Ferreira JR, dos Santos CM, Macedo LE, de Oliveira RB, Rodrigues JA (2006). Estradiol reduces cumulative mercury and associated disturbances in the hypothalamus-pituitary axis of

- ovariectomized rats. *Ecotoxicology and Environmental Safety* 63:488-493.
- Packera RJ, Cohen BH, Cooney K (2000). Intracranial Germ Cell Tumor. *The Oncologist* 4:312-320
- Pinheiro MC, Crespo-Lopez ME, Vieira JL, Oikawa T, Guimaraes GA, Araujo CC (2007). Mercury pollution and childhood in Amazon riverside villages. *Environment International* 33:56-61.
- Pluschke A (2013). Primary intracranial germinoma. *Journal Pathology* 45:79-80.
- Reddy MP, Saad AF, Doughty KE, Armstrong D, Melguizo-Gavilanes I, Cheek BS, Opatowsky MJ (2015). Intracranial germinoma. *Proc (Bayl Univ Med Cent)*. 28(1):43-45.
- Rodríguez EM, Medesani DA, Fingerman M (2007). Endocrine disruption in crustaceans due to pollutants: A review. *Comparative Biochemistry and Physiology, Part A*, 146:661-671.
- Shankar S, Wu X, Kalra VB, Huttner AJ, Malhotra A (2016). Ectopic intracranial germinoma. *Journal of Clinical Neuroscience* pp. 192-195.
- Vasiljevic A, Szathmari A, Champier J, Fèvre-Montange M, Jouvét A (2015). Histopathology of pineal germ cell tumors. *Neurochirurgie* 61(3):130-137.
- Welling R, Beaumont JJ, Petersen SJ, Alexeeff GV, Steinmaus C (2015). Chromium VI and stomach cancer: a meta-analysis of the current epidemiological evidence. *Occupational and Environmental Medicine* 72(2):151-159.
- Yuan W, Yang N, Li X (2016). Advances in Understanding How Heavy Metal Pollution Triggers Gastric Cancer. *BioMed Research International* 2016.