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Neuro-immunological effects of fluorosis: Current perspectives and future outlook for Saudi Arabia

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ABSTRACT

Fluorosis severely affects the quality of life of people causing metabolic and degenerative disorders. Its alarming upsurge in the recent years is a matter of deep concern and warrants intense research to completely eliminate this food and water borne ailment. Compelling evidence indicates that fluoride produces injury not only to the central nervous system but also to the immune system which is the first line of defense against xenobiotics. Studies have demonstrated that the intelligence of children and animals exposed to high levels of fluoride caused lowered learning ability and memory. Fluoride causes neuronal destruction and synaptic injury by free radical production and lipid peroxidation. Although limited information is available about immunotoxicity, it is hypothesized that fluoride affects cells of humoral and cell mediated immune responses. In addition, fluoride is reported to decrease white blood cell counts. Though there have been prospective studies in the past which elucidated various aspects of fluoride induced toxicity, the exact comprehensive understanding of the molecular and biochemical mechanisms of fluoride on the neuroimmunological processes is still a subject that needs clinical evaluation. Fluorosis is an endemic problem affecting the quality of life of millions in Saudi Arabia. However, only a few studies are conducted in this region. Owing to its alarming upsurge in recent years, it is important to design future studies to evaluate the neurotoxic and immunotoxic potential of fluoride exposure in humans.

1. Introduction

Water is most common contributor to daily fluoride intake (Nayak et al., 2009) presumably resulting from the use of soil or fertilizer-borne fluoridated water for processing (EFSA, 2013). Almost all foods contain trace amounts of fluoride as it is ubiquitous in the environment (Ayoob and Gupta, 2006). Fluorides are also released into the environment during the production of aluminium and the manufacture of phosphate fertilizers (WHO, 2002). Moreover, fluoridated dental products include dentifrices (toothpastes, powders, liquids, etc.,) for home use and various gels and other topical applications for use in dental offices. Highly substantial associations were found between fluoride ingestion from toothpaste and fluorosis (Bhagavatula et al., 2016). In the fluoridated brands, this concentration further raises the fluoride levels to 1000-4000 ppm (ADA, 2005). Complexes of fluoride with aluminum (AlF_3 or AlF_4) or beryllium (BeF^-3) in addition to fluoroaluminate complexes and fluorosilicic acid or sodium fluosilicate, Na_2SiF_6 are commonly found in the environment (WHO, 2002). Fluoride research in the past decades suggests that concentrations below 1 ppm are beneficial in the prevention of dental caries or tooth decay, but above 1.5 ppm increases the severity of the incurable disease fluorosis. Dental fluorosis, skeletal fluorosis, distribution in soft tissues, urinary tract manifestations, allergies, gastro-intestinal side effects and neurological manifestations are caused due to excess fluoride levels (WHO, 2002). While dental fluorosis can result in loss of dental function when severe, a condition associated with long-term exposure to fluoride resulting in fragile bones having low tensile strength leads to skeletal fluorosis. Four stages of this affliction have been defined, encompassing a preclinical stage and three clinical stages that characterize the severity (ATSDR, 2013).

It is important to note that excess fluoride ingestion over a period of time can affect the structure

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and function of biological systems resulting in a variety of clinical manifestations. The rates of delivery are generally determined by the blood flow to well-perfused tissues causing steady-state fluoride concentrations between plasma and tissues such as the heart, lungs and liver rapidly than between plasma and tissues such as resting skeletal muscle, skin and adipose tissue. Fluoride is concentrated to high levels within the kidney tubules, so this organ has a higher concentration than plasma (Karaoz et al., 2004). The regular intake of fluoride rich products is thought to affect the neurological system leading to nervousness, depression, polydypsia and polyurea amongst others.

2. Is fluorosis a global issue?

Millions of men, women and children in many countries of the world are affected by fluorosis and many of them are crippled and lead vegetative life (FAN, 2012). Fluoride research in so far suggests that concentrations below 1 ppm are beneficial in the prevention of dental caries or tooth decay, but above 1.5 ppm increases the severity of the incurable disease fluorosis (Carey, 2014; Kanduti et al., 2016). This incurable disease continues to be a major public health problem. Fluorosis is endemic in many parts of the world particularly in middle latitude regions and its severe form; skeletal fluorosis has been reported world-wide. WHO estimates about 2.7 million people with skeletal fluorosis in China (WHO, 2002). Over 6 million suffer this crippling bone disease in India (FAN, 2012). Fluorosis as the sign of fluoride overload is endemic in at least 25 nations across the world and in many continents.

3. Scenario in Saudi Arabia

UNICEF reports that groundwater with more fluoride concentrations are found in can be Middle East (UNICEF, 2008). The assessment of fluorosis from Saudi Arabia has been limited to not many studies. In the book 'Fluoride in drinking water' from WHO, Hail region over 90% of 2355 rural children reported dental fluorosis and a strong association has been shown between fluoride levels and severity. The holy city Mecca has been reported to have endemic fluorosis. Fluorosis in Saudi Arabia is considered to be an endemic problem (Dhaar, 2008). Dental fluorosis is amongst one of the most prevalent health effects observed in Saudi Arabia (Siddiqui et al., 2017). However, currently only a single clinical trial is underway that is recruiting subjects for the assessment sodium fluoride in dentin hypersensitivity (NCT02936830) and no studies are being conducted with focus on neuro-immunological effects.

4. Why are studies on neuro-immunological effects of fluoride exposure important?

Studies in animals and human populations suggest that fluoride exposure through fluoridated drinking water may have severe effects on the developing brain. Epidemiological studies and animal experiments have demonstrated that the intelligence of children and animals exposed to high levels of fluoride caused lowered learning ability and memory. In a recent study by Trivedi et al. (2007) reported that the mean IQ level of students exposed to high F drinking water was significantly lower than that of the students exposed to a lower F level drinking water. There is very little information about the immunotoxic effects of fluoride in the scientific literature. Among the limited available literature, it had been proposed that fluoride could induce humoral immunity leading to antibody production (Das et al., 2006). The exact mechanism of the neuro-immunotoxic effect of fluoride complexes on the brain has not been fully elucidated, although there is evidence that it is closely related neurotoxicity caused by heavy metals and a host of neuropathological conditions (Sharma et al., 2014; Shivarajashankara and Shivashankara, 2012).

5. Neuro-immunological effects

Fluoride is hypothesized to cause disruption of the structure and functions of the brain, further leading to reductions in the metabolic activity. Epidemiological studies and animal experiments have demonstrated that the intelligence of children and animals exposed to high levels of fluoride were severely impaired, especially with the symptoms of decreased learning ability and memory. Yet, studies indicate that high levels of fluoride in drinking water ranging from 3-11ppm affect the nervous system directly without causing skeletal fluorosis (Valdez-Jiménez et al., 2011). There is also evidence that learning and memory processes are affected by high fluoride exposure. Several studies appeared from China which indicated a lowering of I.Q associated with fluoride exposure (Xiang et al., 2003; Xiang, 2003).

Fluoride has been thought to cause an increase in the incidence of allergic diseases through immunomodulatory effects. De Vos et al. (2004) investigated their potential allergy-promoting activity. Fluoride seems to selectively suppress Th1 activity and stimulate Th2 cytokine production in vitro. There is very little information about the immunotoxic effects of fluoride in the scientific literature. Among the limited available literature, it had been proposed that fluoride could induce humoral immunity (Das et al., 2006). To date, there is a dearth of knowledge about the *in vivo* immuno toxic effects of all fluoride containing products.

6. Mechanisms in fluoride-induced neuro-immunotoxicity

Fluoride has been shown to cause neuronal destruction and synaptic injury through free radical production and lipid peroxidation. The exact mechanism of the neurotoxic effect of fluoride and complexes on the brain has not been fully elucidated, although there is evidence that it is closely related to that of heavy metal neurotoxicities as well as a host of neuropathological conditions (Blaylock, 2007). The

common mechanisms which are involved in inducing fluoride toxicity are free radical generation, inhibition of antioxidant enzymes, inhibition of mitochondrial energy enzymes and inhibition of glutamate transporters.

Extensive research on fluoride induced immunotoxicity has so far been able to demonstrate the possible effects of fluoride on IgG levels. Additionally, some reports also showed that the differential counts of lymphocytes, monocytes, and neutrophils decreased significantly in fluoride-treated rats consistent with those reported earlier (Deng et al., 2016; Gutowska et al., 2015). Because fluoride can cause reactive oxygen species generation, it has been suggested that these effects on leukocytes could be due to an induced oxidative stress. Besides affecting the cells of the CMI and HMI, several studies also report that fluoride induces adverse hematological effects thereby damaging the hematopoietic organs (Eren et al., 2005). These studies hint at the possibility that excess fluoride intake not only causes various neurological and other physiological damage but also inflicts severe immunotoxic effect on various cells of the immune system thereby making the population highly vulnerable for various metabolic and immune disorders.

7. Molecular aspects of fluoride induced neuro-immunotoxicity

Fluoride can cause various effects at a cell and molecular level through its interaction with enzymes either through stimulation or suppression of enzyme activity, in addition to inhibiting protein metabolism and causing alteration in cell signalling pathways. At the level of transcription, fluoride is thought to act as a modulator and also a regulator for gene expression (Barbier et al., 2010). In vitro studies in animal cells indicate that fluoride exposure increases NF-kB production and decreases neural cell adhesion molecules in primary rat hippocampal neurons (Zhang et al., 2008). Moreover, an increase in apoptosis molecules like Fas, Fas-L, Caspase-3 and Caspase-8 were found in neuroblastoma cells (Zhang et al., 2007). In vivo human studies on peripheral blood mononuclear cells from individuals drinking water with fluoride showed a decrease in inflammatory chemokines, CCL-1, CCL-18 and CCL-19, a decrease in IL-11 and IL-2 along with a decrease in pro-inflammatory and anti-inflammatory and apoptosis markers (Salgado-Bustamante et al., 2010).

8. Treatment options and modalities for fluorosis

Studies have indicated that fluoride levels beyond the threshold values is toxic and over a long period of time can cause dental, skeletal, and non-skeletal fluorosis. Subjects with compromised nutritional status especially with deficiencies in antioxidants and minerals, pre-existing medical conditions, very young and patients with kidney and heart problems are unusually susceptible to fluorosis (Dhar and Bhatnagar, 2009). While dental fluorosis is largely taken care by aesthetic improvements to the teeth, specific therapeutic regimens are not available for skeletal fluorosis (Khairnar et al., 2015). Prevention and minimizing the exposure levels can go a far way to mitigate most effects of fluoride toxicity. Some reports indicate that ingestion of calcium, vitamin C, and vitamin D can protect from fluoride toxicity. Methionine in combination with Vitamin E has been shown to be efficacious in skeletal fluorosis. While choline has been shown to induce a protective effect against fluoride in animal studies (Zhao et al., 2017), taurine is thought to restore renal function after fluoride exposure (Adedara et al., 2017). In addition, *Punica granatum* juice has been shown to mitigate the oxidative stress in rats (Bouasla et al., 2016) and Cistanche is thought to alleviate symptoms of fluorosis.

9. Need for additional studies

Studies suggest that fluoride exposure, at levels present in fluoridated drinking water may have adverse impacts on the developing brain. Epidemiological studies and animal experiments have demonstrated that the intelligence of children and animals exposed to high levels of fluoride were severely impaired, especially with the symptoms of decreased learning ability and memory. In a recent study by Trivedi et al. (2007) reported that the mean IQ level was lower in students exposed to high levels of fluoride in drinking water. There is very little information about the immunotoxic effects of fluoride in the scientific literature. To date, there is a dearth of knowledge about the *in vivo* immuno toxic effects of the compounds of fluoride. The exact neurotoxic mechanism of fluoride on the brain has to be fully elucidated (Blaylock, 2007). Though there have been several prospective studies in the past which elucidate various aspects of fluoride induced toxicity, none of these studies have been able to comprehensively demonstrate the effect of fluoride on the neurotoxic and immunotoxic aspects of fluoride exposure.

10. Recommendations and future perspectives

Biological markers (biomarkers) are needed as integral tools in monitoring the health effects and in evaluating risk factors associated with exposure to fluoride. Evaluations of molecular and biochemical mechanisms that seek to understand the toxic effects of fluoride exposure are the need of the hour. The effects of fluoride on subjects showing fluorosis in Saudi Arabia that is increasingly the site of high exposure to this chemical by virtue of using this compound in many industrial chemicals are absolutely required. The use of population screening programs in which individuals are screened and analyzed to know the effects that signify relative levels of exposure and the role of fluoride as neurotoxic and immunotoxic chemical are required for appropriate observations and inferences to be drawn from these studies. In addition, the use of simple, well established protocols will facilitate interpretability and reproducibility of the expected results in short periods of time.

The authors recommend the need for high end research in case-control studies in fluorosis affected patients and healthy controls.

11. Conclusion

Fluorosis in Saudi Arabia is considered to be an endemic problem (Dhaar, 2008). In fact, UNICEF reports that groundwater with more fluoride concentrations are found in the Middle East (UNICEF, 2008). However, the assessments of fluorosis from Saudi Arabia have been limited to only a few studies. Fluorosis is an important predicament severely affecting the quality of life of millions and ultimately causing several metabolic and degenerative disorders. Its alarming upsurge in the recent years especially in tropics is a matter of deep concern and warrants intense research to completely eliminate this ailment.

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Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

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