Volume 07, Issue 05 (September-October 2024), PP 59-66 www.ijmsdr.org
ISSN: 2581-902X

International Journal of Medical Science and Dental Research

Neurotoxicity of Fluoride: A Narrative Review

*Subhashree T[1], Yashoda R[2], Manjunath P. Puranik[3]

[1,2,3]*Department of Public Health Dentistry, Government Dental College and Research Institute, Bangalore-560002, Karnataka, India*

***Corresponding author: Subhashree T,**
Postgraduate student, Department of Public Health Dentistry, Government Dental College and Research Institute, Fort, Victoria Hospital campus, Bengaluru, Karnataka 560002 India.

Abstract : *Fluoride, an essential trace element and is crucial for skeletal metabolism and dental remineralization in humans. Excess fluoride consumption is linked to various adverse health effects impacting multiple organ systems. This review aimed to consolidate evidence on fluoride's systemic and neurotoxic effects. Fluoride's neurotoxic effects are well-documented, showing an inverse relationship between fluoride exposure and intelligence. Children in high-fluoride areas have significantly lower IQs compared to those in low-fluoride areas. The mechanisms of fluoride's neurotoxicity involve oxidative stress, apoptosis, enzyme inhibition, altered metabolic pathways, DNA and RNA synthesis inhibition, excitotoxicity, and effects on nerve impulse transmission. Though there is evidence linking fluoride exposure to reduced IQ, establishing a causal relationship remains challenging due to the multifactorial nature of intelligence. Further longitudinal studies are necessary to investigate the confounders such as genetics, environment, and nutrition. The review emphasizes the need for continued research and public health measures to mitigate adverse impacts of fluoride.*

Keywords - *Fluoride, Neurotoxicity, Intelligent Quotient*

I. BACKGROUND

Fluoride plays a crucial role in promoting skeletal metabolism and dental remineralization. However, prolonged and excessive intake over a long period may cause major health disorders such as dental fluorosis, skeletal fluorosis and non-skeletal fluorosis.[1]

The distribution of fluoride in the natural environment is very uneven. India is situated in the geographical fluoride belt and in areas where fluoride content is high in rocks or soil, leaching of fluoride occurs, causing excess fluoride level in groundwater. Almost two-third states in India fall into this belt making fluorosis one of the severe public health problems in India. Approximately 25 million people are presently affected by fluorosis and 66 million are at risk of developing fluorosis, including children of age 14 years.[2]

Besides dental and skeletal fluorosis, the excess fluoride consumption promotes hip fracture, leads to still birth or birth defects, and has detrimental neurological effects.[3] Studies have found that chronic fluorosis can cause brain damage, resulting in abnormal brain structure and brain function. Chronic fluorosis not only

Volume 07, Issue 05 (September-October 2024), PP 59-66 www.ijmsdr.org
ISSN: 2581-902X

causes a decline in concentration, learning, and memory, but also has mental symptoms such as anxiety, tension, and depression.[4] These neurotoxic effects of fluoride are more profound in children, since the capacity of the developing brain to detoxify is lower, and it is more vulnerable to toxicants than the mature brain.

Studies across the world have shown chronic exposure to high levels of fluoride as one of the factors that influence intellectual development.[5]

Numerous studies have identified chronic exposure to high fluoride levels as a factor influencing intellectual development. This review aims to consolidate evidence on the systemic effects of fluoride, mainly focusing on its neurotoxic impacts in humans. The review would also discuss the adverse effects on various parts of the brain and nervous system, ultimately leading to impaired intelligence.

II. FLUORIDE – THE DOUBLE-EDGED SWORD

Fluoride (F), an essential trace element, can be a double-edged sword because of its beneficial and damaging effects on teeth. Fluoride has a significant mitigating effect against dental caries, if the concentration is approximately 1mg/l. Whereas fluoride above a threshold concentration has been shown to be toxic.[6] The WHO's drinking water quality guideline value for F is 1.5 mg/L. However, WHO emphasizes that in setting national standards for F it is particularly important to consider climatic conditions, volumes of water intake, and intake of F from other sources (e.g., food and air).[7]

III. ADVERSE EFFECTS OF FLUORIDE

The safe dose range of fluoride is found to be limited.[8] The toxicity of fluoride due to excessive ingestion is classified into acute toxic effects and chronic effects.[9] Table 1 shows the effects of fluoride based on dose of exposure.[10]

Concentration or dose of F (ppm)	Frequency	Effects
0	Daily for years	Increased susceptibility to dental caries
1-2 (1 ppm in water)	Daily for years	Reduced dental caries (greatest effect from pre-eruptive dosage)
3-15 (2-10 ppm in water)	Daily for years	Dental fluorosis of varying severity and frequency (pre-eruptive dosage only). Reduced caries
20-80	Daily for 8 or more years	Crippling skeletal fluorosis, gastric disturbances. Dental fluorosis (pre-eruptive dosage). Reduced caries

250-1000	One retained dose	Nausea, vomiting
3,000-10,000	One retained dose	Probable death

Table 1: Effects of fluoride based on dose of exposure.

Acute toxicity

According to WHO, Acute toxic doses range from 1 to 5 mg/kg. Such doses could be expected from water with a fluoride content of approximately 30 mg/l (WHO, 2000). Doses exceeding 15 to 30 mg/k may be fatal.

Signs and symptoms of acute systemic fluoride intoxication are increased salivation, lacrimation, severe nausea, vomiting, diarrhoea, muscular fibrillation, and respiratory, cardiac, and general depression and abdominal pain. In severe or fatal cases, these symptoms are followed by convulsions, cardiac arrhythmias, and coma.[11]

Chronic toxicity

Prolonged exposure to higher concentrations of fluoride can cause chronic toxicity which is irreversible.[12] The known detrimental systemic effects of fluoride include,

- dental and skeletal fluorosis
- renal failure
- gastrointestinal
- neurological
- endocrine and
- carcinogenic impacts.

Dental and skeletal fluorosis: Dental Fluorosis, a cosmetic effect, occurs due to elevated fluoride levels during enamel development. It ranges from subtle porosity in the outer enamel to market staining or pitting in severe cases, with the increased severity affecting both depth and degree of porosity.[1] Endemic skeletal fluorosis is associated with higher levels of fluoride exposure, resulting in osteosclerosis, ligamentous and tendinous calcification and extreme bone deformity.[13]

Renal effects: Prolonged exposure to fluoride (8 ppm or higher) has been reported to increase renal diseases. The kidney plays an important role in fluoride excretion (50-60% excretion). It is affected due to the uptake of fluoride within the kidney tubules. Increased levels of serum creatinine and urea nitrogen may occur due to swelling, degeneration of tubular epithelium, fibrosis, atrophy of glomeruli, and tubular necrosis may occur.[9]

Gastrointestinal effects: High concentration fluoride reacts with gastric acid to form hydrogen fluoride which irritates the gastric mucosa. Non-ulcer dyspeptic symptoms may appear when exposed to more than 3.2ppm of fluoridated water.[9]

Respiratory effects: A longitudinal study performed on aluminium potroom workers showed F as an important risk factor for developing asthmatic symptoms. 3.4 and 5.2 times higher odds were seen in the medium- and high-exposure groups, respectively, than in the low exposure group.[13]

Endocrinal effects: A meta-analysis showed an association of increasing fluoride concentrations with decreasing birth rates that was attributed to effect of high fluoride ingestion on males, such as the morphology and mobility of sperm, the levels of testosterone, follicle- stimulating hormones and inhibin-B.[14]

IV. FLUORIDE ON NERVOUS SYSTEM

Certain animal studies have documented fluoride toxicity to brain cells using high fluoride concentrations. Around 0.5 μmol/L and 3 μmol/L of F has been found to induce lipid peroxidation and inflammatory reactions in brain cells respectively. These concentrations are similar to the ranges of serum fluoride levels reported in the human population.[15]

The effect of fluoride on nervous system can be due to

- Neurological manifestations of skeletal fluorosis
- Fluoride accumulation in brain
- Alterations in brain cell health
- Disrupted metabolism in brain
- Adverse influence on antioxidant system in brain
- Mental functions

Neurological manifestations of skeletal fluorosis: Neurological symptoms of skeletal fluorosis like tingling sensation in the fingers and toes, nervousness depression, paralysis of the limbs, vertigo, spasticity in the extremities, and impaired mental acuity.[16]

Fluoride accumulation in brain: Fluoride crosses the Blood Brain Barrier and accumulates in the hippocampus of brain, which is closely related to functions such as learning, memory and emotion.[4,17]

Alterations in brain cell health: Chronic fluoride intoxication alters the brain cell architecture. Animal studies have shown that the ultrastructure of hippocampus had pathological changes in the neurons, synapses along with myelin damage.[4] The mitochondria and endoplasmic reticulum (ER) in neurons were damaged along with increased intracellular lipofuscin. The neuronal synapses were swollen and the mitochondria were degenerated.[18]

Disrupted brain metabolism: Fluoride inhibits enzymes concerned with the metabolism of proteins, amino acids and free radicals. Hence it is a metabolic poison that alters the metabolic pathways in the liver, muscle and the brain.[19]

Adverse influence on antioxidant system in brain: The decreased levels of antioxidants may attribute to their depletion on combating the reactive oxygen species which are generated in chronic fluoride toxicity.[20]

Mental functions: Brain tissues such as cerebral cortex, hippocampus, and cerebellum are closely related to learning, memory, emotion, and behavior, and their structural alterations may affect the brain activities.[19] Many studies have shown that the children in fluorosis endemic areas are prone to mental retardation and that their IQ is low.[19]

Patients with chronic fluorosis could manifest mood disorders such as anxiety, depression and thinking difficulties.[21] Residents of fluorosis areas tend to exhibit more social anxiety, reduced life satisfaction, and higher depression compared to those in normal areas.[16]

V. MECHANISM OF NEUROTOXICITY OF FLUORIDE

Fluoride causes neurotoxicity through various mechanisms like,

- Oxidative stress
- Effect on apoptosis
- Inhibition of enzymes
- Altered metabolic pathways.
- Inhibition of DNA and RNA synthesis.

- Excitotoxicity
- Effect on excitability

Oxidative stress

The primary hotspot involved in the neurotoxicity of fluoride is oxidative stress. Fluoride may induce free radicals generation resulting in the consequent oxidative stress.[22]

Effect on apoptosis

Fluoride can induce apoptosis in hippocampal neurons which could be due to elevated oxidative stress.[22] The ER (Endoplasmic Reticulum) stress leading to neurodegeneration and cognitive dysfunction plays an important role in fluoride-induced toxicity. The ER stress and associated apoptotic signaling are involved in fluoride-induced neurotoxicity.

Inhibition of enzymes

Fluoride at small concentrations affects the activities of enzymes like cholinesterase, glutamine synthetase, catalase, alkaline phosphatase, phosphorylase, acid phosphatase, pyrophosphatase, aconitase, esterases, creatine phosphokinase, muscle ATPase, glucuronidase, phosphomutase, enolase, succinate dehydrogenase, adenyl cyclase, cytochrome c, lactate dehydrogenase, and carboxylase. Some enzymes such as pyrophosphatase, acetylcholinesterase, glucose-6-phosphatephosphohydrolase in the presence of aluminum ions, and lactate dehydrogenase are inhibited by fluoride, while others, such as adenylate cyclase, are activated.[15,23]

Altered metabolic pathways

Fluoride disrupts energy generation, membrane function, amino acid metabolism and nerve impulse transmission. It alters glucose, lipids and amino acid metabolism.[23]

Inhibition of DNA and RNA synthesis

Fluoride is found to induce DNA damage in the brain. Sodium fluoride can affect the peptide chain initiation and in turn disrupt cellular protein synthesis.

Excitotoxicity

Baylock proposed the theory of excitotoxicity as a mechanism in the neurotoxicity of fluoride.[24] Excitoxicity is caused due to the overstimulation of the glutamate receptors in the neurons, leading to microglia activation (the immune cells of the brain). Microglia releases cytokines and other immune factors that cause brain cell death. The cascade of excitoxicity is mediated through the reactive oxygen species (ROS) and the reactive nitrogen species (RNS).[3]

Effect on excitability

Prolonged exposure to high levels of fluoride may inhibit cholinesterase and impair nerve impulse transmission. This affects brain activity.[25]

VI. FLUORIDE AND INTELLIGENCE

Intelligence is an important dimension of an individual's personality. The widely accepted definition is that it is the ability to see meaningful relationships between things. Intelligence includes perceiving, knowing, reasoning and remembering. It is believed that intelligence is a result of an interplay between hereditary and environmental factors. Genetic and environmental factors may have a major effect on intelligence.[26]

A minimum of 2-4 mg/l of fluoride level is required to cause a neurotoxic response. Fluoride influences the reaction times and visuospatial capabilities, thus lowering the IQ scores during the time sensitive tests.[9]

Children living in endemic fluoride belt are found to have five times higher odds of having low IQ compared to those who live in low or normal fluoride levels.[27]. Similar findings were in another study[28] that children living in endemic fluorosis areas possessed lower intelligence quotient (IQ) scores than those from normal areas and suggested an inverse association between fluoride exposure and children's intelligence. Studies[8,12,29,30] have also reported a negative dose response relationship of fluoride exposure and dental fluorosis (DF) with intelligence quotient (IQ). Increased fluoride exposure correlates with higher DF grades and lower IQ scores. Children with dental fluorosis exhibited significantly lower IQs, suggesting that excess fluoride negatively impacts intellectual development.

VII. CONCLUSION

The developmental neurotoxicity associated with fluoride has been gaining attention recently. This necessitates identifying the critical windows of vulnerability to fluoride exposure for promoting child health. Evidence suggests that the developing brain has increased sensitivity to environmental toxicants. The excess uptake of fluoride can disrupt the functions of various enzymes and proper metabolic and physiological activities. Excess fluoride may affect brain activity and inhibition of cholinesterase leading to a breakdown in nerve impulse transmission. It may also lead to altered cognitive function and psychiatric symptoms such as anxiety and depression. All these events may potentiate the risk of developing reduced IQ associated with fluoride exposure during fetal and infant development.

Although evidence suggests a relationship between fluoride and IQ, there is a lack of studies proving a causal relationship. IQ is influenced by multiple factors such as genetics, environment, and nutrition. To address these confounders, longitudinal studies are needed to identify and control these factors. Additionally, further toxicity studies are necessary to evaluate fluoride's potential harm to various organ systems.

REFERENCES

[1] Fejerskov O, Manjp F, Baeluw V. The Nature and mechanisms of dental fluorosis in Man. J Dent Res. 1990;69:S692-700.

[2] Verma A, Shetty B K, Guddattu V, Chourasia M K, Pundir P. High prevalence of dental fluorosis among adolescents is a growing concern: A school based cross-sectional study from Southern India. Environ Health Prev Med. 2017;22:17.

[3] Sebastian S T, Sunitha S. A cross-sectional study to assess the intelligence quotient (IQ) of school going children aged 10-12 years in villages of Mysore district, India with different fluoride levels. J Indian Soc Pedod Prev Dent. 2015;33:307-11.

[4] Ren C, Li H H, Zhang C Y, Song X C. Effects of chronic fluorosis on the brain. Ecotoxicol Environ Saf. 2022;244:114021.

[5] Poureslami H R, Horri A, Khoramian S, Garrusi B. Intelligence quotient of 7 to 9 year-old children from an area with high fluoride in drinking water. J Dent Oral Hyg. 2011;3:61-64.

[6] Till C, Green R, Flora D, Hornung R, Mier A M, Blazer M et al. Fluoride exposure from infant formula and child IQ in a Canadian birth cohort. Environ Int. 2020;134:105315.

[7] Kundu H, Basavaraj P, Singla A, Gupta R, Singh K, Jain S. Effect of fluoride in drinking water on children′s intelligence in high and low fluoride areas of Delhi. J Indian Assoc Public Health Dent. 2015;13(2):116-21.

[8] Xu K, An N, Huang Hui, Duan L, Ma J, Ding J et al. Fluoride exposure and intelligence in school-age children: evidence from different windows of exposure susceptibility. BMC Public Health. 2020;20:1657.

[9] Ullah R, Zafar M S, Shahani N. Potential fluoride toxicity from oral medicaments: A review. Iranian Journal of Basic Medical Sciences. 2017;20:841-8.

[10] Dunning JM. Principles of Dental Public Health. 4th ed. Harvard University Press. 1986.

[11] WHO. Environmental health criteria 36. Fluorine and Fluorides. 1984;1-99.

[12] Manveen K, Kulkarni S. Relation between dental fluorosis and Intelligence Quotient of school children in Nagpur - A Cross-Sectional Study. Glob J Res Anal. 2020;9(5):127-31.

[13] WHO. Air quality guidelines, chapter 6.5 fluorides. Reg Off Eur. Copnhagen, Denmark. 2nd ed, 2000:1–9.

[14] Ozsvath D L. Fluoride and environmental health: A review. Rev Environ Sci Biotechnol. 2009;8:59–9.

[15] Grandjean P. Developmental fluoride neurotoxicity: An updated review. Environmental Health. 2019;18:110.

[16] Nakamoto T, Ralph Rawls H. Fluoride exposure in early life as the possible root cause of disease in later life. J Clin Pediatr Dent. 2018;42(5):325-30.

[17] Vani M L, Reddy P. Effects of fluoride accumulation on some enzymes of brain and gastrocnemius muscle of mice. Research Report. 2000;33(1):17-26.

[18] Niu R, Chen H, Manthari R K, Sun Z, Wang J, Zhang J et al. Effects of fluoride on synapse morphology and myelin damage in mouse hippocampus. Chemosphere. 2018;194:628-33.

[19] Shivarajashankara Y M, Shivashankara A R, Rao S H, Bhat P G. Oxidative stress in children with endemic skeletal fluorosis. Fluoride. 2001;34(2):103-7.

[20] Gao Q, Liu Y-J, Guan Z-Z. Decreased learning and memory ability in rats with fluorosis: increased oxidative stress and reduced cholinesterase activity in the brain. Fluoride. 2009;42(4):277-85.

[21] Spittle B. Psychopharmacology of fluoride: a review. Int Clin Psychopharmacol. 1994;9:79–82.

[22] Zhang M, Wang A, He W, He P, Xu B, Xia T et al. Effects of fluoride on the expression of NCAM, oxidative stress, and apoptosis in primary cultured hippocampal neurons. Toxicology. 2007;236:208-16.

[23] Kaminsky L S, Mahoney M C, Leach J, Melius J, Miller M J. Fluoride: benefits and risks of exposure. Crit Rev Oral Biol Med. 1990;1(4):261-81.

[24] Haripriya B, Pratyusha P, Madhavi O, Reddy K , Hema N, Samyuktha C L. Comparative study of dental fluorosis with Intelligent Quotient (IQ) in school children in Chittoor District. Int J Sci Res 2020;9(6):71-3.

[25] Ren D, Li K, Liu D. A study of the intellectual ability of 8-14 year-old children in high fluoride, low

iodine areas. Fluoride. 2008;41(4):319-20.

[26] Park K. Park's Textbook of Preventive and Social Medicine. Bhanot Publishers. India. 26th ed. 2021.

[27] Yani S I, Seweng A, Mallongi A, Nur R, Abdullah M T, Salmah U et al. The influence of fluoride in drinking water on the incidence of fluorosis and intelligence of elementary school students in Palu City. Gac Sanit. 2021;35:S159-63.

[28] Trivedi M H, Verma R J, Chinoy N J, Patel R S, Sathawara N G. Effect of high fluoride water on intelligence of school children in India. Fluoride. 2007;40(3):178-83.

[29] Wang S, Zhao Q, Li G, Wang M, Liu H, Yu X et al. The cholinergic system, intelligence, and dental fluorosis in school-aged children with low-to-moderate fluoride exposure. Ecotoxicol Environ Saf. 2021; 228:112959.

[30] Xiang Q, Liang Y, Chen L, Wang C, Chen B,Chen X et al. Effect of fluoride in drinking water on children's intelligence. Fluoride. 2009;36(2):84-94.