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The Impact of Fluorosis in Neurological Disorders: A Mini-Review

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Abstract

The purpose of the present review is to update and conclude available evidence of risk of fluorosis associated with neurological disorders. Neurological disorders are diseases of the central and peripheral nervous system which includes the brain, spinal cord, cranial nerves, peripheral nerves, nerve roots. Alzheimer disease, dementia, Parkinson's disease, neuropathy, Autism, and memory and learning deficits are considered as neurological disorders. Globally 47.5 million people are affected by dementia and 7.7 million new cases are found every year. Alzheimer's disease is the main reason for developing dementias in 60–70% of cases. Fluorosis is a metabolic bone disease which is produced due to prolonged exposure to excessive amounts of fluoride through various sources. Extreme fluoride exposure may possibly consequence to central nervous system dysfunction. Chronic fluorosis might play a role in Alzheimer's disease, as it is common among people living in endemic fluorosis regions. High levels of fluoride exposure may have the risk of impaired intelligence in children. Excessive ingestion of fluoride leads to calcification of ligaments and tendons causes compression on nerve structures and produces myelopathy and radiculopathy. Fluoride can cross the blood-brain barrier especially at the time of pregnancy period leading to develop neural deterioration of offspring which promotes learning and memory impairments. The present review attempts to elucidate the possible relationship between fluorosis and neurological disorders.

Keywords:
Fluorosis, Alzheimer's disease, Dementia, Neurodegeneration.

Introduction

Fluorosis, as a universal public health crisis, has received extensive and deserving awareness in recent years. Fluoride contaminated water is the reason for occurring 80% of diseases and fluoride pollution is the main cause to develop 65% of endemic fluorosis in the world [1]. In India 62 million people including 6 million children are affected with fluoride related health diseases. Epidemiological studies in China have shown that, about 330 million people are exposed to high fluoride, among them about 42 million are

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suffering from fluorosis [2]. Fluoride exposure leads to dental and skeletal fluorosis. Fluoride has been shown to be toxic, not only to the teeth and skeletal tissues, but also to the non-skeletal tissues such as the brain, liver, pancreas, endocrines, and the kidney [3]. Dental fluorosis causes mottling of enamel of the teeth, however skeletal fluorosis is characterized by swollen, deformed joints and enlarged bones. Fluoride is a neurotoxic agent and scientific interest of effect of fluoride, its mechanism on the nervous system has been increasing recently [4]. Fluoride toxicity showed a several types of neuropsychiatric symptoms which include drowsiness, confusion, learning and memory disorders [5]. Present review focused on the neurological diseases which are born due to fluoride exposure.

Methods

The following search engines like Google Scholar, ScienceDirect, Web of Science, PubMed/Medline and Research Gate were used to collect data as evidence from already published literature.

Effect of fluorosis on Alzheimer's disease (AD)

Alzheimer's disease (AD) is a progressive neurodegenerative disease which Impaired short term memory and decline cognitive ability. AD Patients complaints confusion, disturbances of language, sleep-wake cycle and gradual development of long-term memory loss [6]. Accumulation of neurofibrillary tangles and amyloid plaques are the pathological basis of AD [7]. Amyloid plaques are produced from β-amyloid peptides (Aβ), which are formed by the enzymatic cleavage of the amyloid precursor protein (APP) [8]. AD patients exhibit severe memory deficits, these deficits were associated with changes in hippocampal synaptic transmission, particularly with changes in synaptophysin expression [9]. Acetylcholine (ACh) plays a significant role in cognitive processes and disturbance of cholinergic system produces Alzheimer's dementia in AD patients [10]. In AD predominantly neurodegenerative changes take place in hippocampus, frontal cortex, amygdala, nucleus basalis, and medial septum of brain [11].

Chronic fluorosis causes neurodegenerative diseases like Alzheimer's dementia and learning and memory impairments [12]. Metals like aluminum have permeability to cross blood brain barrier and nonmetals like fluoride also have ability to cross blood brain barrier and damage the brain and develops memory and cognitive impairments [13]. Fluoride exposure increases the synthesis of reactive oxygen species by microglial activation resulted oxidative stress [14]. Fluoride stimulates cytokine secretion, macrophages and microglia results neuroinflammatory process in AD [15]. Fluoride plays a significant role in apoptosis which is the main pathogenesis factor in neurodegenerative diseases like Alzheimer's and Parkinson's disease [16]. Long term ingestion of fluoride could affect potential increase in the level of oxidative stress in the brain tissue [17]. Chronic exposure of fluoride decreases the glutathione levels in mice due to oxidative stress [18]. Brain antioxidant enzyme glutathione level was significantly depleted in Alzheimer's patients when compared to normal subjects in non-Invasive Technique study [19]. Fluoride Decreases Acetylcholine Levels when exposed to Fluoridated water [20]. One previous study reported decreased levels of the neurotransmitter acetylcholine in Alzheimer's disease and acetylcholine considered as a neuropathological marker in Alzheimer's disease [21]. Previous studies reported that fluoride induced oxidative stress, and neurodegeneration can be reduced by supplementation of AChE inhibitors [22]. Fluoride exposure causes impaired learning and memory capabilities which involve endoplasmic reticulam stress and associated apoptosis in the hippocampus of rats [23]. The endoplasmic reticulum is the key element involved in protein folding and secretion and is significantly affected in Alzheimer's disease neurons [24]. Fluoride has a possible action to cause nervous tissue degenerative changes in Alzheimer's disease [25]. Dementia is a clinical condition which affects cognitive functional ability and memory impairment due to neurodegenerative and cerebrovascular processes of brain [26]. Chronic administration of fluoride led to inclusions in the blood

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vessels that can cause vascular dementia [27]. A cross-sectional study resulted out of 160 people 67 developed primary degenerative dementia when exposed to highest fluoride concentrations in public water supplies [28].

Effect of fluorosis on Myelopathy

Spinal fluorosis leads to compressive myelopathy, mostly affecting the cervical and dorsal spine of vertebral column. Stenosis of spinal canal is the reason for compressive myelopathy that is due to ossification of ligamentum flavum, and ossification within the dura mater [29,30]. Previous study resulted in 63.63% of cases observed ossification of the interosseous membrane, 33.33% of cases noticed ankylosis and 90.9% cases noticed increased density of bone due to spinal fluorosis [31]. 82% of patients of Indian population the main source of fluoride in take is through deep bore well groundwater [32,33]. Fluorosis is the uncommon cause for developing compressive myelopathy. One study reported ossification of intraosseous membrane in forearm causes compressive myelopathy along with elevated urine fluoride level due to fluoride exposure [34]. Spinal fluorosis causes compression of the nerve roots that results in Neurological manifestations in myelopathy and neuropathy [35]. MRI scan report showed degenerative changes throughout the spine in one fluorosis case that developed compression of spinal cord at multiple levels causes paraplegia [36]. Fluoride in take in endemic areas causes vertebral osteosclerosis that resulted in spinal cord compression [37]. Myelopathy was noticed due to spinal cord compression in 77-year-old man by skeletal fluorosis [38]. Spina bifida is the congenital neural tube defect which affects posterior wall of vertebrae of the spine. Spina bifida is the condition where the patient complains about neuropathological symptoms. Study reported endemic fluorosis areas are more prone to develop Spina bifida occulta in children. One study revealed out of 50 children in 22 (44%) cases noticed spina bifida occulta in the lumbosacral region [39].

Effect of fluorosis on Intelligence quotient (IQ)

Intelligence quotient (IQ) of children depends on environmental, nutritional, and hereditary factors. Chronic ingestion of excess fluoride also results in reduction of intelligence quotient (IQ) in children [40]. High concentration of fluoride in drinking water is the risk factor for impaired intelligence and development in children [41]. IQ scores of children living in fluorosis endemic villages were found to be less compared to the children living in non-endemic villages of India [42]. A meta-analysis of 27 cross-sectional studies of children conducted in China reported exposed to fluoride in drinking water suggests an average IQ reduction of about seven points in children [43]. A comparative study confirmed that average IQ scores were significantly less in children living in the fluorosis endemic area [44]. Children who are exposed to excessive fluoride may be prone to impaired intelligence [45]. Children living in medium and severe fluorosis regions showed less IQ than the children in mild fluorosis region suggesting that excessive fluoride intake is linked with lower intelligence [46]. Exposure of high fluoride levels was related to high rates of mental retardation and borderline intelligence in children [47]. The fluorosis in India is nearly estimated to affect 66.6 million people of which an estimated 6 million are children below the age of 14 years [48].

Effect of fluorosis on Memory and Learning disorder

Extreme exposure to fluoride may generate central nervous system dysfunctions [49]. Sustained exposure to fluoride was the main reason for neuronal activity instability and moreover the unusual behavioral patterns [50]. Chronic fluoride ingestion affects brain, spinal cord and causes neurodegeneration leading to learning and memory impairments [51]. The incidence of learning and memory deficits were typically due to exposure of 100 part per million of fluoride in 30 days of period [52]. Exposure to fluoride in Industrial workers resulted in diminished psychomotor performance and memory [53]. Fluoride exposure affects neuronal differentiation, migration and synaptogenesis leads to learning and memory disturbances [54].

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Perinatal fluoride exposure in male rats showed decreased motor coordination and learning and memory deficits and showed lack of habituation, failure to discriminate between familiar and novel objects in female rats [55]. Fluoride has a role in memory and learning impairments because it releases oxygen free radicals by disrupting oxygen metabolism [56]. Fluoride toxicity could have developed in learning and memory deficits due to a decrease in the nicotinic acetylcholine receptors [57]. High fluoride and arsenic co-exposure in rats showed decreased learning, memory, and biochemical indices [58]. Rats exposed to fluoride revealed the differences in the cognitive responses and deficits in behavioral patterns.

Effect of chronic fluorosis on psychiatric disorders

Patients exposed to chronic fluorosis would manifest psychiatric symptoms such as mood swings, anxiety neurosis and mental depression due to neurotoxicity of brain, so it is required more focusing and consideration [59]. According to previous epidemiological data people living in fluorosis prone places were more likely to showed high prevalence of mental depression and social anxiety and exposure to fluoride in early life can be possible to develop autism and mental retardation disorders [60]. The neuropsychiatric symptoms were noticed more in dental fluorosis patients compared to normal individuals. Previous studies reported that college students suffering from dental fluorosis were showed mild depression and dental fluorosis would be the risk factor for neuropsychiatric depression disorder [61].

Mechanism of action of fluorosis on neurological disorders

Fluorosis may be involved in damaging the brain neurons by various mechanisms. Fluoride can absolutely interact with antioxidant enzymes and decline their ability to scavenge free radicals. Fluoride accumulation in the brain in chronic fluorosis can lead to rapid increased ROS concentrations, reduction in antioxidant enzyme activity, and increased lipid peroxidation process. This mechanism was studied in cerebrum, cerebellum, and medulla, when exposed to 50 and 150 mg/L fluoride in drinking water [62]. Rats exposed to 13 mg/kg of fluoride water every 24 h were noticed altered mitochondrial membrane potential and integrity of neurons due to increased ROS synthesis and lipid peroxidation [63,64]. Brain injury due to fluoride induced oxidative stress is the main mechanism caused in neurological disorders.

Conclusion

Chronic fluorosis disease can cause brain damage by accumulation of fluoride in brain by crossing through the placental barrier or Blood Brain Barrier leads to neurotoxicity and developed cognitive impairment and neuro psychiatric symptoms. Present review concluded fluoride exposure through various sources can affect the nervous system and developed neurological disorders in human and animals according to previous published literature.

Conflict of Interest

None

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