Neuro-medical complications of fluoride toxicity among populations living in fluoride endemic region of the Ethiopian Rift Valley

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Abstract

Background: Fluorosis is endemic in many countries of Asia, South America and Africa. In Africa, the countries located across the Great East African Rift Valley, including Ethiopia are a hotspot for fluorosis. While excessive and chronic exposure to fluoride causes dental and skeletal fluorosis, emerging studies have shown its adverse health effects in cognition, memory, learning and the function of Central Nervous System. Method: We conducted a study on 318 individuals living in rural villages located in fluoride endemic areas of the Ethiopian Rift Valley. Drinking water samples were collected from 23 community well sites, and analyzed for fluoride concentrations. Detailed clinical evaluations of skeletal fluorosis, neurologic history, and physical examination were performed in the study participants. Results: The mean age of the study participants was 28.0±14.9 years. About 80% of the participants were from the communities with fluoride level >2 mg/L. The mean fluoride level in drinking water samples was 6.8±4.3 (range: 0.3 to 15.5 mg/L). Male accounted 55.7% of the subjects participated. Among the neurologic complications, headache, fatigue, and paresthesia accounted for 67%, 56.3%, and 37.5%, respectively. Urinary incontinence, muscle atrophy and crippling neuroflourosis were observed only in a few of our study participants (< 5%). Headache disorders had statistically significant association with high fluoride levels. Clinical anemia was observed in 49.7% of our study population. Conclusion: Fluorosis has significant socio-economic and psychological impacts on productive segment of a population. Unlike previously reported findings, where neurological complications were largely attributed to compressive radioculomyelopathy, this study highlighted toxic level of fluoride might also results in non-compressive neurological and medical complications. We therefore recommend conducting further large scale epidemiological study to confirm these findings.

Background

Fluoride (F^-) is one of the chemicals that commonly found in the environment and known to cause adverse effects in human health, primarily from exposure to naturally contaminated drinking-water sources. According to the WHO, more than 200 million people worldwide rely on drinking water with fluoride concentrations exceeding the recommended level of 1.5mg/L **[1].** Fluoride has beneficial effects on teeth often at recommended exposure concentrations of below 1.5mg/L in drinking-water **[2]**. On the contrary, excessive exposure to fluoride in drinking-water, or other sources, can give rise to a number of adverse health effects. These conditions range from mild dental fluorosis to crippling skeletal fluorosis, which depends on the fluoride level and duration of exposure time. Crippling skeletal fluorosis is a significant cause of morbidity **[3]**.

One of the well-known regions associated with active volcanic activity is located across the East African Rift countries including Ethiopia, Uganda, Kenya and Tanzania. Many of the lakes in the Rift Valley system, especially the soda lakes of Elmentaita and Nakuru in Kenya have extremely high concentrations of fluoride, 1,640 mg/L and 2,800 mg/L, respectively **[4]**. In Ethiopia, over 20 million people are living in

the Rift Valley areas, which increase their risk of fluorosis, and related complications **[5]**. In a study in Ethiopia Rift Valley region, from a total 1438 surface and ground water samples, 24.5% had flouride concentration above 1.5 mg/L the optimal concentration recommended by World Health Organization **[6].**

The prevalence of dental and skeletal fluorosis in the Ethiopian Rift Valley was estimated to be 80% and 45%, respectively **[7, 8, 9].** Animal and human studies supported the adverse effect of fluoride on human central nervous system. A study by Yu et al, **[10]**, on human brain tissues from aborted fetuses from endemic fluorosis areas showed fluoride can accumulate in brain tissue and affect the synthesis of certain neurotransmitters and receptors in nerve cells that lead to damages to nerve cells **[10].** Waldbott et al. **[11]**, reported prevalence of migraine-like headaches to be 50% among individuals exposed to chronic fluoride. He analyzed 112 cases from the four different regions around the world for pre-skeletal clinical signs and symptoms of skeletal fluorosis. Accordingly, cervical and lumbar spine arthritic pain accounted for 42%, epigastric pain, nausea and vomiting, accounted 51%, while Dermatitis, accounted for 4% **[11].**

According to a recent experimental study, the neurotoxic changes in the brain of the rabbits indicated apoptosis of the neurones and neuroglial cells due to fluoride toxicity. The data suggests that there is a direct action of fluoride in high dosage level on the nerve tissue, which is responsible for paralysis, seizure, tremors, and sensory deficits and is indicative of brain dysfunction **[12].** High levels of fluoride in drinking water (3-11 ppm) are also known to directly affect the central nervous system and cause intellectual disability and behavioral abnormality without first causing the physical deformities of skeletal fluorosis **[13, 14].** Toxic level of fluoride in human body causes neurologic disorders, as well as various medical disorders, including, hypothyroidism, polyuria, polydipsia, hearing difficulty, and dyspepsia **[15].**

The objective of this study is to assess neurological features in populations of the Ethiopian Rift Valley chronically exposed to wide-ranging concentrations of fluoride (0.3 to 15.5 mg/L) in drinking water from community-based wells. We evaluated the associations between variation in F^{-} in drinking water and different clinical symptoms of skeletal fluorosis. The symptoms include 1) Early signs of skeletal fluorosis such as loss of appetite, nausea, headache, and pallor, 2) Skeletal changes, such as difficulty to touch chest with chin, difficulty of bending forward and touching the toes, and difficulty to sit in squatting position, and 3) physical examination including limitation of movements at the joint (wrist, elbow, shoulder, neck, knees, ankle), bowing of legs, and knocked knee.

Methods

1.1. Study area

The study area lies in the Ethiopian Rift Valley, which is part of the Great East African Rift Valley, which bisects the northeastern side of the African continent. The rift floor and the plateaus to the east and west that border the Rift floor have average altitudes of 1600 m and 2500 m above sea level (m.a.s.l.), respectively. The climate is semi-arid to arid in the Rift Valley, and the mean annual temperature on the Rift floor exceeds 20 °C **[16].**

1.2. Sampling and measurement of flouride in water samples

We selected 23 water sampling sites based on previous research data collected on fluoride levels in water sources of the study region, which identified wide variation in exposures to fluoride (ranging from 0.3 to 15.5 mg/L) from water extracted from groundwater wells used for drinking and cooking **[17-18].** Water fluoride content was determined using the ion selective electrode, buffering the standards and water samples using equal volume ratios with a total ionic strength adjustment buffer (TISAB II). This allows optimal analysis of fluoride ion by adjusting the pH of the solution between 5 and 5.5, and the ionic strength of the standards and samples to the same values. Calibration standards were prepared from a 100 mg/L stock solution. The range of electrode calibration slope for a 10-fold change in fluoride concentration was−57 to −60 mV, which is within the acceptable range. The accuracy of ISE fluoride measurements for water standards ranged from 98% to 102.5% relative to the standard. The detection limit of the fluoride electrode is 0.02 mg/L.

1.3. Study population and neurological examination

The survey questionnaire was conducted in face-to-face interviews by using field enumerators (Ethiopian graduate students and nurses/medical doctors), who were trained on the content of the questionnaire. A total of 318 individuals aged between 10-70 years old were enrolled in selected 23 rural villages that have their respective drinking water wells. Comprehensive physical examination, with emphasis on neurological examination was done for all study participants by certified neurologist. All the examination findings were recorded on structured questionnaire. The neurological assessment included, examination of mental state, cranial nerves, motor, tone, reflex, sensory, and gait. The following physical examination were done to assess for signs of skeletal fluorosis: ability to touch chest with chin, bending forward and touching the toes, and sitting in squatting position, limitation of movements at the joint (wrist, elbow, shoulder, neck, knees, ankle) and any signs of bowing of legs, and knocked knee.

1.4. Methodology used to assess clinical signs of anemia in study population

We have evaluated the study participants for clinical signs of anemia by checking for pallor in the following area: conjunctiva, finger nails and tongue to diagnose anemia. Diagnosing anemia in developing countries such as Ethiopia is difficult because of limited laboratory facilities. However, many

studies supported the use of physical examination as a means of diagnosing anemia in resource limited settings **[29-30].**

1.5. Statistical analysis

Demographic data, signs and symptoms of skeletal fluorosis, medical and neurological complications and fluoride exposure variables were first described by their quartiles, means, and standard deviation. Association between different level of flouride concentrations and different variables were done using chi square, adjusted odds ratio (OR) and p value was set at < 0.05 as statistically significant.

Results

1.1. Frequency of socio-demographic variables and distribution of fluoride in water.

The age of our study participants ranged between 10 to 70 years, with a mean age of 28.0+14.9 years. Two-hundred two (63.5%) of our study participants were between the age 15 and 44 years. A little more than half of the study participants (55.7%) were males. The mean water flouride level was 6.8+4.3 mg/L, out of 318 study participants, 20.1% had water fluoride < 2mg/L, while 51. 6% had fluoride concentration between 6-16 mg/L **[Table 1].**

1.2. Pre-skeletal complications of fluorosis in study subjects.

We screened the study participants for pre-skeletal features of fluorosis. Out of 318 participants, 158 (49.7%) had clinical signs of anemia, evidenced by pallor on physical examination. Loss of appetite, constipations, and nausea were reported in 48.1%, 45.3% and 28.9%, respectively. Excessive thirst and urination reported by 6.6% of study participants **[Table 2].**

1.3. Clinical signs of skeletal fluorosis among study participants.

Prevalence of clinical signs related to skeletal fluorosis was evaluated among the study participants, 71(22.3%) had impaired lumbar mobility, 21 (6.6%) had impaired squatting, 18(5.7%) had bow legs, 7(2.2%) had impaired neck mobility, 6(1.9%) had kyphosis and 5(1.6%) had knocked knee **[Table 3].**

1.4. Observed neurologic complications among study participants.

Neurologic signs and symptoms related to chronic fluoride toxicity was evaluated among our study participants. Sixty seven percent (n=213) of participants reported that they are suffering from headache. Thirteen (4.1%) of our study participants had a rigid posture and bended at their neck, while 3(0.9%) of the participants walk with stick support. Hundred-ninety (37.5%) reported paresthesia of extremities, while urinary incontinence and muscle atrophy were observed in 2 (0.6%) and 6(1.8%), respectively **[Table 4].**

1.5. Association between fluoride concentrations and headache disorder

Evaluation of the association between different fluoride concentrations in drinking water and occurrence of headache disorders showed that exposure to higher concentration of fluoride in drinking water (10-15.5 mg/L) had statistically significant association with headache disorder ($p<0.05$) **[Table 5].** While fluoride concentration < 2mg/L did not show statistically significant association. This suggested that headache disorder is more common among study participants who are exposed to higher concentration of fluoride in drinking water. Moreover, those individuals with fluoride exposure in drinking water between 10-15.5 mg/L are 2 times more vulnerable to develop headache than the baseline exposure (<2mg/L), *[Crude OR (95% of CI), 3.52(1.67-7.39)]* **[Table 5].**

Paresthesia of extremities showed statistically significant agreement with higher concentration of fluoride (*p = 0.03).* Moreover, signs of crippling neuroflouorosis, such as walking with one stick and rigid posture and bending at neck spine also showed statistically significant association with higher concentration of fluoride in drinking water, *(p <0.05)* **[Table 6].** Study participants who drinks water containing fluoride concentration between >10-15.5 mg/L, were ten times more prone to develop rigid posture and bending at neck spine compared to individuals who are exposed to low concentration of fluoride in drinking water (< 2 mg/L) **[Table 6].** We evaluated association between different fluoride concentrations and some of the clinical signs of skeletal fluorosis such as impaired lumbar mobility and kyphosis, which showed statistically significant association with higher fluoride concentration in drinking water (>10-15.5mg/L) *(P <0.05)*, while impaired squatting did not (p = 0.9) **[Table 7].** Fluoride concentration >10-15.5mg/L, was found to have statistically significant association with loss of appetite, nausea and constipation, but not with clinical signs of anemia. Among 49.7% participants who had clinical signs of anemia, only 22.4% used water source containing fluoride concentration < 2mg/L, whereas 81.6% of them used water wells containing flouride concentration > 2mg/L [**Table 8].**

Discussion

This study is part of a cohort of individuals who are part of a study initiated in Ethiopian Rift Valley with the aim of understanding skeletal and non-skeletal complications of chronic fluoride toxicity. The first case of neurological complications of severe fluoride toxicity was reported in Ethiopia 45-years back by Lester, et al, 1974 **[19]**, who reported a case of fluoride myelopathy. Since then population-based studies in the Ethiopian Rift Valley were focused on dental, skeletal, and a few on neurological complications of chronic fluoride intoxication **[17, 18, 20].** The mean age of our study participant was 28.0±14.9 (range: 10-70 years) and men-to-women ratio was 1.2:1. The mean fluoride concentration in water samples was 6.8 ± 4.3 mg/L, which is 4.5 times the WHO recommended level **[1].** Only 20.1% of water samples had fluoride concentration below 2mg/L. In the previous work, we found statistically significant association between fluoride in drinking water and in urine **[27]**, indicating that fluoride in drinking water is the main source of fluoride exposure in the study region.

Clinical signs of anemia based on evidences of pallor, were observed in close to half of our study participants, which are consistent with study reported by Erdal et, al, 2005, which revealed that the rate of anemia in children living in the fluoride endemic region was 2.4 times greater than children living in non-

fluoride endemic regions **[21].** Moreover, study done in Malawi reported: pallor of the conjunctiva, tongue, palm or nail beds was 66% sensitive and 68% specific in distinguishing children with moderate anemia *(hemoglobin concentration, 5-8g/dl)* and 93% sensitive and 57% specific in distinguishing those with severe anemia (hemoglobin concentration, <5 g/dl), even without laboratory support, which is often unavailable in rural Africa **[31].**

It is well documented that different gastrointestinal (GI) symptoms of GI irritation, including nausea, loss of appetite and abdominal pain is common in endemic fluorosis with populations chronically exposure to higher concentration of fluoride **[22, 23]**. This is consistent with our study findings that showed loss of appetite, constipations and nausea were reported in 48.1%, 45.3% and 28.9%, respectively **[Table 2].** Loss of appetite, constipation and nausea had statistically significant association ($p<0.05$) with higher fluoride concentration **[Table 8].**

A study by Assefa et al, (2004), on skeletal fluorosis among retired employees of wonji-shoa sugar estate in Ethiopia, prevalence of skeletal fluorosis was found to be, 20% and 70%, respectively **[24]**.The authors reported impaired squatting in 39%, impaired neck mobility in 29% and impaired lumbar mobility in 40.2% of the subjects **[24]**. Compared to their study, our study showed lower prevalence of clinical signs of skeletal fluorosis. This is likely because their study participants mean age was 55-years and they only selected individuals having signs and symptoms of skeletal fluorosis, which likely increased the prevalence of skeletal fluorosis. Among clinical signs of skeletal fluorosis, impaired lumbar mobility and kyphosis showed statistically significant ($p <0.005$) association with higher concentrations of fluoride, while impaired squinting did not ($p<0.86$) **[Table 7].**

The involvement of the nervous system in skeletal fluorosis was reported in India as early as 1937 and skeletal fluorosis is associated with neurologic complication in 3-10% **[25, 28].** In Ethiopia, neurological complications of chronic fluoride toxicity had a pattern of radiculo-myelopathies in 80% of individuals suffering from skeletal fluorosis, in which 66% involves cervical region **[20].** Most of previously reported studies on fluoride toxicity largely attribute neurological complications of chronic fluoride intoxication to mechanical compression of the spinal cord and nerve roots by skeletal fluorosis, rather than direct neurotoxic effect of higher fluoride exposure **[26]**. However, number of recent publication reported, high levels of fluoride in drinking water (3-11 ppm) are known to affect the central nervous system and can cause intellectual disability and behavioral abnormality without first causing the physical deformities of skeletal fluorosis **[14,15]**.

We observed higher prevalence of headache disorders (67%) among our participants. Our finding is consistent with a study reported by Waldbott et al (1998), where 50% of 112 cases of skeletal fluorosis complained of headache **[11].** We also found statistically significant association between headache and higher concentration of fluoride in drinking water compared to low fluoride concentration **[Table 5].** We found 37.5% of our study participants reported paresthesia of extremities, which is in line with study done in India were some of their patients having skeletal fluorosis reported paresthesia **[11].** Evidences of crippling neuroflourosis *(walking with one stick and rigid posture and bending at neck spine)* were

observed in 13 (4%) study a participant, likely indicating advanced skeletal and neurological complications of fluoride toxicity often occurs in older patients after decades of exposure to high fluoride water. Signs of rippling neuroflourosis showed statistically significant association with higher concentration of fluoride in drinking water **[Table 6].** We have identified the following limitations to our study: absences of controlled group for comparison, relatively small sample size compared to total number of people exposed to toxic dose of fluoride, and failure to use standard laboratory measuring methods, eg. not using hemoglobin measurements while assessing anemia.

Conclusions

Our findings strongly suggest the adverse neurological and medical effects associated with prolonged exposure to elevated concentrations of fluoride in drinking water. We recommend conducting large scale epidemiological study in fluoride endemic areas using controlled population to better understand non-skeletal fluorosis related to neurological and medical complications.

Abbreviations

F^-: Fluoride, **ERV**: Ethiopian Rift Valley, **Mg/L**: Milligram per liter, **WHO:** World Health Organization, **GI**: Gastrointestinal, **PPM**: Parts per million (ppm)

Declarations

Ethics approval and consent to participate:

The study received ethical approval from the Institutional Review Board (IRB) at Tulane University (Protocol No. 2018-043) and locally from the National Research Ethics Review Committee (NRERC) (reference no. MoSHE/144/1096/19). All subjects provided written consent, and parents/guardians gave permission for children to participate in addition to children giving their own assent.

Consent to publish:

All authors agreed on the decision to publish this manuscript. Participants consent for publication is not applicable.

Availability of data and materials:

All data sets on which the conclusions of the manuscript rely are available as spread sheets documents and available from the corresponding author on reasonable request from the journal editors.

Competing interests:

The authors declare that they have no competing interests.

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This is part of an ongoing cohort study in the Ethiopia Rift Valley with a long-term goal of understanding the health impacts of fluoride in teeth, cartilage, joint, and bone mineralized tissues and associated neurologic complications of fluoride related health problems in children and adults. We are immensely grateful for the funding from the NIEHS's career development grant (K99/R00 ES023472).

Authors Contributions:

BA, YM, RT, and TR participated in data acquisition, data analysis, data interpretation and manuscript editing and preparation and all authors have read and approved the manuscript before submission.

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Tables

Table 1: Frequency of socio-demographic variables and distributions of fluoride.

		Frequency	Percent
Fluoride level	Mean±SD	6.8±4.3	
	<2 mg/l	64	20.1
	≥2-6 mg/l	90	28.3
	≥6-10 mg/l	87	27.4
	≥10-16 mg/l	77	24.2
Age group	Mean±SD	28 ±14.9	
	<15	67	21.1
	≥15-24	103	32.4
	≥25-34	44	13.8
	≥35-44	55	17.3
	≥45	49	15.4
Gender	Male	177	55.7
	Female	141	44.3

Table 2: Frequency of medical complications in study participants

		Frequency	Percent
Loss of appetite	Yes	153	48.1
	No	165	51.9
Nausea	Yes	92	28.9
	No	226	71.1
Constipation	Yes	144	45.3
	No	174	54.7
Fatigue	Yes	179	56.3
	No	139	43.7
Clinical signs of Anemia	Yes	158	49.7
	No	160	50.3
Excess thirst and urination	Yes	21	6.6
	No	297	93.4

Table 3: Frequency distribution of clinical signs of skeletal fluorosis.

		Frequency	Percent
Impaired lumbar mobility	Yes	71	22.3
	No	247	77.7
Impaired neck mobility	Yes	7	2.2
	No	311	97.8
Impaired squatting	Yes	21	6.6
	No	297	93.4
Knocked knee	Yes	5	1.6
	No	313	98.4
Bow legs	Yes	18	5.7
	No	300	94.3
kyphosis	Yes	6	1.9
	No	312	98.1

Table 4: Frequency of neurological complications among study participants.

		Frequency	Percent
Headache	Yes	213	67.0
	No	105	33.0
Paresthesia of extremities	Yes	119	37.5
	No	199	62.5
Urinary incontinence	Yes	2	0.6
	No	316	99.4
Walking with one stick	Yes	3	0.9
	No	315	99.1
Rigid posture and bending at neck spine	Yes	13	4.1
	No	305	95.9
Muscle atrophy	Yes	6	1.8
	No	313	98.2

Table 5: Association between fluoride concentration and headache.

		Headache		Crude OR (95% of CI)
		Yes (%)	No (%)	
Fluoride level (mg/L)	<2	28(43.8)	36(56.2)	1.00
	>10-15.5	57(74.0)	20(26.0)	3.52(1.67-7.39)**

***=p<0.05*

Table 6: Association between fluoride concentration and neurological complications.

		Fluoride level (mg/L)				p-value
		<2	>2-6	>6-10	>10-15.5	
Paresthesia of extremities	Yes	14(11.8)	35(29.4)	35(29.4)	35(29.4)	0.03
	No	50(25.1)	55(27.6)	52(26.1)	42(21.1)	
Walking with one stick	Yes	0	0	0	3(100)	0.03
	No	64(20.3)	90(28.6)	87(27.6)	74(23.5)	
Rigid posture and bending at neck spine	Yes	0	0	3(23.1)	10(76.9)	0.002
	No	64(21.0)	90(29.5)	84(27.5)	67(22.0)	

Table 7: Association between flouride concentration and signs of skeletal fluorosis.

		Fluoride level (mg/L)		p-value
		<2	>10-15.5	
Impaired lumbar mobility	Yes	27(38.0)	21(29.6)	0.001
	No	37(15.0)	56(22.7)	
Impaired squatting	Yes	3(14.3)	6(28.6)	0.90
	No	61(20.5)	71(23.9)	
kyphosis	Yes	0	5(83.3)	0.01
	No	64(20.5)	72(23.1)	

Table 8: Association between flouride concentration and pre-skeletal signs and symptoms.

		Fluoride level (mg/L)		p-value
		<2	>10-15.5	
Loss of appetite	Yes	17(11.1)	42(27.5)	0.01
	No	47(28.5)	35(21.2)	
Nausea	Yes	9(9.8)	24(26.1)	0.02
	No	55(24.3)	53(23.5)	
Constipation	Yes	14(9.7)	35(24.3)	0.005
	No	50(28.7)	42(24.1)	
Clinical signs of anemia	Yes	29(18.4)	39(24.7)	0.86
	No	35(21.9)	38(23.8)	

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- STROBEchecklistFluorosis.doc