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The continuing crippling challenge of skeletal fluorosis – Case series and review of literature

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ABSTRACT

Background: Skeletal fluorosis is a metabolic bone disease that results from the chronic ingestion of fluoride. Although there are national programs in place to raise awareness and curtail this disease condition, skeletal fluorosis continues to cause crippling deformities in areas where it continues to be endemic.
Method: ology: An observational study was undertaken at a university-affiliated teaching hospital in southern India. Clinical, biochemical features and densitometric variables including bone mineral density (BMD) and trabecular bone score (TBS) were assessed.
Results: All patients (n = 9) hailed from fluorosis-endemic Indian states and the source of drinking water was from a bore-well in all cases. The mean (±SD) age and BMI were 45.6(±11.0) years and 25.6 (±8.4) kg/m^2 respectively. Dental mottling was present in five subjects. Five subjects each had vitamin D deficiency with osteomalacia. The mean (±SD) urine fluoride was 2.9(±1.4) ppm. The bone mineral density showed a sclerotic pattern, with the mean (±SD) TBS being 1.607 (±0.160). All patients were initiated on calcium and cholecalciferol supplements and those with osteomalacia were treated with calcitriol.
Conclusion: While fluorosis continues to be a challenge in endemic regions, the presence of osteomalacia proves to be a treatable component of the disease condition. There seems to be an unmet need for more aggressive defluoridation techniques and the provision of safe drinking water in susceptible individuals.

1. Introduction

Skeletal fluorosis (SF) is a metabolic bone disease caused by the chronic ingestion or rarely by the inhalation of fluoride ions in areas where high levels of fluoride occur naturally [1]. It may often be asymptomatic and discovered incidentally on radiological examination or may present with myriad manifestations that include diffuse skeletal pain, limited mobility, or osteopenia with the ossification of many ligaments and interosseous membranes [2].

Skeletal fluorosis may develop gradually over decades from chronic exposure to fluoride and its effect on the bone depends on the amount ingested and the duration of exposure [3]. Rarely, rapid development of fluorosis has been reported with chronic fungal prophylaxis with voriconazole [4] or the abuse of inhalants such as dichlorodifluoromethane [5]. The fluoride that enters the food chain by consumption of fluoride rich products is absorbed through the gastrointestinal tract and enters the skeleton where it has a half-life of more than seven years [6]. Fluoride is incorporated in the hydroxyapatite crystal [3] and affects the strength of the bone, influences bone remodeling through Runt-related transcription factor 2(Runx2) and Receptor activator of nuclear factor kappa-B ligand (RANKL) and alters the expression of osteocalcin and osteoprotegerin with increase in osteoblastic activity [7].

Clinical features include dental mottling, bony pains, chronic fatigue, joint stiffness with restricted range of motion, flexion contractures, the development of radiculo-myelopathy and an increased risk of fracture [8]. Thus far, no treatment has been found to be effective in established skeletal fluorosis. Management consists of symptomatic treatment with analgesics and provision of adequate calcium and vitamin D nutrition. Decompressive laminectomy may be performed for relief of neurological deficits due to involvement of the spine [9].

Skeletal fluorosis is thus a disabling condition which continues to be endemic in some parts of the world. India is one of the 25 countries around the world, where it was first described in the 1930s. Although there has been a national programme for the prevention and control of

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fluorosis in the country, the population at risk is officially estimated to be about 11.7 million who lack access to safe drinking water [10]. There is limited data on the varied clinical manifestations relating to skeletal fluorosis in adult patients from India. In this study, we describe the clinical features, bone biochemistry, radiology and densitometric parameters including bone mineral density (BMD) and trabecular bone score (TBS) in adult patients diagnosed to have skeletal fluorosis presenting to the metabolic bone disease unit of a tertiary care centre in India.

2. Methods

This was an observational study done at a university affiliated teaching hospital in southern India. The details of patients were obtained from January 1, 2015 to December 31, 2019, through the Computerized Hospital Information and Processing System (CHIPS), which includes a clinical workstation (CWS) and a picture archiving and communications systems (PACS). The access to CWS is authenticated by a password. Consent has been obtained from each patient after full explanation of the purpose and nature of all procedural investigations used.

A diagnosis of skeletal fluorosis was made based on characteristic imaging features that included osteosclerosis, ligamentous calcifications most evident on the pelvis and spine, trabecular blurring or haziness, and ossification of tendon attachments or muscles, interosseous membrane, and posterior longitudinal ligament of the spine with the detection of excess urinary fluoride in urine. The particulars of the patient including demography and clinical profile, biochemistry, treatment and outcomes were obtained. Clinical features that included bony pains, joint stiffness, difficulty in ambulation, muscle weakness, mottling of dental enamel, presence of deformities and neurological deficits were obtained from the archived medical records. X-ray images, DXA reports and available bone scintigraphic images were obtained through the PACS.

Blood biochemical data were collected which included alkaline phosphatase (N: 40–125 IU/L), albumin-corrected calcium (N: 8.3–10.4 mg/dL), phosphate (N: 2.5–5 mg/dL), 25-hydroxy Vitamin D (Vitamin D) (N: 30–75 ng/mL), creatinine (N: 0.6–1.2 mg/dL), parathormone (N:8–84 pg/mL) and urine fluoride (N: <1 ppm), was assayed by ion specific electrode (Thermofisher scientific).

Subjects underwent DXA scanning in the Hologic Discovery A (S/N 83624) with APEX software Version 13.4.2:3 for bone mineral density (BMD) measurements at the lumbar spine and femoral neck. The CV of BMD assessment at the femoral neck was 2–3% and at the lumbar spine was <1%. Trabecular Bone Score (TBS) is a non-invasive method that evaluates pixel gray level variations in the lumbar spine DXA image and helps in assessing the microarchitecture of the bone. TBS was assessed using iNsight Software version 3 (Med-Imaps, Bordeaux, France) [11]. The CV of assessment of TBS was <1%. The study was approved by the institutional review board (IRB) of Christian Medical College, Vellore, India.

3. Results

3.1. Demographic details and clinical features at presentation

A total of 9 patients were diagnosed to have skeletal fluorosis of which five were males. Six patients were from the Indian states of Jharkhand, Bihar and West Bengal and the remaining three were from the southern states of Tamil Nadu, Karnataka and Telengana. The mean (SD) age and BMI were 45.6(11.0) years and 25.6 (8.4) kg/m^2 respectively. The source of drinking water was from a borewell in these patients. All patients presented with low back ache. Dental mottling (Fig. 1) was present in five patients. The other clinical manifestations are shown in Table 1. The median duration of symptoms was 11 years (range: 4–16 years).

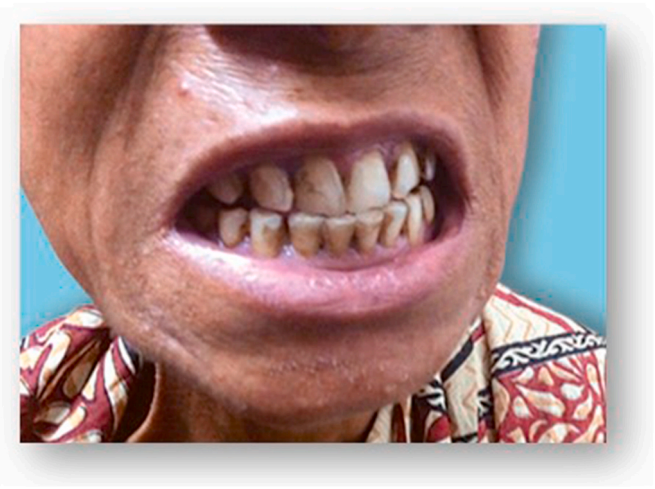

Fig. 1. Dental mottling.

3.2. Bone biochemistry

Among the nine subjects with fluorosis, 5/9(Patient Number 1 to 5) (55.5%) had vitamin D deficiency and 4/9 (44.4%) had secondary hyperparathyroidism. Five patients(Patient Number 1 to 5) were also noted to have a component of osteomalacia as reflected by the elevated alkaline phosphatase. The mean(SD) urine fluoride was 2.9(1.4) ppm. The other bone biochemical parameters and urine fluoride are depicted in Table 2.

3.3. Radiology

The typical findings of fluorosis demonstrable on radiology were as follows:

a. Diffuse osteosclerosis and calcification of posterior longitudinal ligament (Fig. 2A)
b. Insufficiency fractures (Fig. 2B)
c. Sand-like striations involving scapulae and ribs (Fig. 2C)
d. Calcification of attachment of muscles and ligaments (Fig. 2D)
e. Interosseous membrane calcification (Fig. 2E)
f. Diffuse osteopenia and trabecular prominence (Fig. 2F)
g. Calcification of sacrotuberous ligaments, sacrospinous ligaments, obturator membrane and adjacent to lesser trochanter (Fig. 2G)

3.4. Densitometric variables

A sclerotic pattern was observed at least at one site in all subjects, (Table 3) whose DXA reports were available. Patient 5 had osteopenia at neck of femur and patient 3 had osteopenia at forearm. Patient 2 had low bone mass (Z score of −4.1) at distal forearm despite having sclerotic bone at other sites(Z score of +5.3 at neck of femur and +6.3 at lumbar spine. The mean(SD) trabecular bone score was 1.607(0.160), which was well above the normal of >1.350.

3.5. Complications and treatment

Two patients in our series had significant compressive myelopathy and were advised surgical decompression. Other associated comorbidities included anemia (5/9), primary hypothyroidism (2/9), chronic kidney disease (3/9), renal tubular acidosis (1/9) type 2 diabetes mellitus (5/9) and hypertension (2/9). All subjects were advised to use safe fluoride free water for drinking and domestic use. All patients received cholecalciferol and calcium supplements. Osteomalacia was treated with calcitriol and co-existent metabolic abnormalities were treated

Table 1
Clinical features at presentation.

Sl no.	Age	Gender	Residence	BMI kg/m^2	Low back ache	Muscle weakness	Joint pains	Joint stiffness	Restriction of movement	Neurological deficit	Deformities	Dental mottling
1	31	F	Bihar	NA	+	+	+	+	+	+	+	+
2	36	M	Bihar	20.8	+	+	+	+	+	+	+	+
3	56	M	West Bengal	21.0	+	+	+	+	+	–	–	+
4	51	M	Jharkhand	23.3	+	+	+	–	+	+	–	NA
5	48	F	Tamil Nadu	NA	+	+	+	+	+	–	–	+
6	47	M	Telengana	25.6	+	+	+	+	+	+	–	+
7	65	F	Karnataka	40.6	+	+	+	+	+	–	–	NA
8	42	F	West Bengal	NA	+	+	+	–	+	+	–	NA
9	34	F	Jharkhand	22.5	+	+	+	+	+	–	+	–

Table 2
Bone biochemistry.

Sl no.	Calcium mg/dL (N:8.3–10.4)	Phosphate mg/dL (N:8.3–10.4)	Creatinine mg/dL (N:0.7–1.2)	PTH pg/mL (N:8–74)	25(OH) vitamin D ng/mL (N:30–75)	Alkaline phosphatase U/L (N:40–125)	Urine fluoride ppm (N:<1 ppm)
1	9.03	3.5	0.5	162.0	12.7	419.0	4.84
2	7.61	4.1	1.3	499.3	18.6	936.0	1.26
3	9.88	3.2	1.6	19.4	17.0	150.0	1.22
4	8.00	2.9	1.7	385.7	3.8	627.0	2.72
5	9.07	1.6	0.8	171.1	4.0	581.0	2.31
6	9.22	3.8	1.1	33.2	37.3	126	3.54
7	8.72	3.2	1.2	46.7	22.6	58.0	1.34
8	9.30	4.2	1.6	49.3	25.4	114.0	4.13
9	8.42	5.4	0.6	58.3	26.2	95.0	2.81

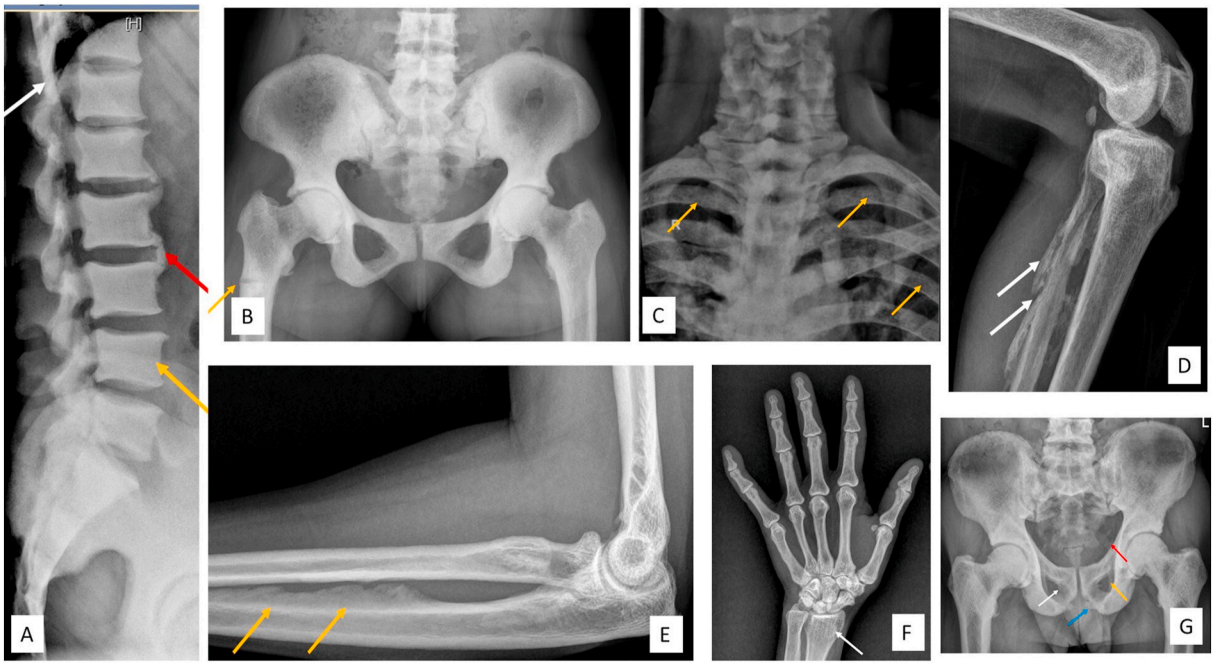

Fig. 2. A: X-ray (lateral view of lumbo-sacral spine) showing diffuse osteosclerosis (yellow arrow), osteophytes (red arrow) and calcification of posterior longitudinal ligament (white arrow). Figure 2BInsufficiency fractures (yellow arrow) involving shaft of right proximal femur. Figure 2CChest X-ray showing sand-like striations involving scapulae and ribs (yellow arrow). Figure 2DX-ray of the leg showing calcification of attachment of muscles and ligaments (white arrow). Figure 2EX-ray of the forearm showing interosseous membrane calcification (yellow arrow). Figure 2FX-ray of the distal forearm showing diffuse osteopenia and trabecular prominence (white arrow). Figure 2GX-ray of the pelvis showing calcification of obturator membrane (white arrow), sacrotuberous ligament (yellow arrow), sacrospinous ligament (red arrow) and tendinous insertion (blue arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Densitometric variables.

Sl no.	BMD (NOF) g/cm^2	NOF (T-score)	NOF (Z-score)	BMD (LS) g/cm^2	LS (T-score)	LS (Z-score)	BMD (FA) g/cm^2	FA (T-score)	FA (Z-score)	TBS
1	1.076	2.1	2.3	2.157	10.4	10.3	NA	NA	NA	NA
2	1.594	4.9	5.3	1.776	6.2	6.3	.578	−4.3	−4.1	1.506
3	1.115	1.4	3.1	2.207	10.1	11.5	.732	−1.6	NA	1.771
4	1.592	NA	NA	NA	NA	NA	NA	NA	NA	NA
5	0.638	−1.9	−0.6	1.120	.7	2.1	NA	NA	NA	1.437
6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
8	1.321	4.3	4.6	2.376	12.1	12.4	.663	-.4	.1	1.715
9	1.071	2.0	2.2	2.143	10.0	10.0	.653	-.7	-.5	1.715

NA- Not available.

optimally.

4. Discussion and review of literature

In this study we describe the clinical features, biochemistry, radiology and densitometric parameters of nine patients diagnosed to have skeletal fluorosis presenting with varied manifestations to a tertiary care centre in southern India. The diagnosis of skeletal fluorosis was made based on characteristic X-ray features of osteosclerosis, inter-osseous membrane calcification and elevated levels of urinary fluoride. All patients hailed from the states that were endemic for fluorosis in the country and the predominant symptom at presentation was low back ache. Five patients had a component of osteomalacia. A sclerotic pattern with high trabecular bone score was noted in subjects with skeletal fluorosis.

Although not a life-threatening condition, significant fluoride accumulation in the body leads to compromised dental aesthetics, skeletal involvement and severe crippling disease which impairs the health-related quality of life in affected subjects. There exists no cure for fluorosis and prevention appears to be the only solution. This is accomplished by the provision of safe drinking water. When the availability of safe water supply cannot be ensured, defluoridation techniques are undertaken and this includes the “Nalgonda” technique, adsorption on activated alumina, electrocoagulation and reverse osmosis. By far, the most popular of these is the “Nalgonda” technique which consists of flocculation, sedimentation and filtration of the fluoride salt by the addition of aluminum sulphate/chloride combined with lime [12,13]. These techniques reduce the concentration of fluoride and make the water safe for human consumption.

Among the subjects diagnosed to have fluorosis, five had evidence of dental fluorosis while all had features of low back ache with muscle weakness, pain and stiffness of joints with restriction of joint mobility. The total quantity of ingested fluoride and duration of exposure are the key factors that decide the clinical course of skeletal involvement. Signs of fluorosis become apparent following constant consumption of more than 8–10 ppm of fluoride in drinking water for 10 or more years. In the early stages of the disease, affected individuals may present with vague aches, muscle weakness and chronic fatigue which may be dismissed as functional symptoms, but may in fact result from fluoride toxicity to tendons and ligaments. In late stages, the bones develop an abnormal crystalline structure, with restriction of movements of bones and joints, limited chest expansion, kyphosis and eventually leaves the patient crippled [8]. Osteosclerosis, osteomalacia and osteoporosis may be encountered with secondary hyperparathyroidism being seen in a proportion of cases [1]. Although there is no cure for skeletal fluorosis, it may be borne in mind that osteomalacia with insufficiency fractures presents a “treatable component” of the disease process and may require active vitamin D (calcitriol) in addition to elemental calcium. Moreover, juvenile skeletal fluorosis may occur in children with an inadequate calcium in the diet, making it imperative to ensure adequate calcium and vitamin D nutrition in all individuals especially growing children [14]. Dental fluorosis occurs due to chronic fluoride intake in the first seven years of life. This manifests as mottling of the dental enamel following which the teeth become hard and brittle with discrete and confluent pitting becoming apparent in the late stages.

Although fluorosis does not directly result in neurotoxicity, neurological manifestations may be noted in severe skeletal fluorosis due to compression of the spinal cord and nerve roots by the osteophytosis; cervical myeloradiculopathy, spastic paraparesis and quadriparesis may develop in advanced cases with grossly reduced antero-posterior diameter of the spinal canal, narrowing of the inter-vertebral foramina, sclerosis of the vertebral column and ossification of the spinal ligaments. Other manifestations include the development of hypothyroidism, anaemia, reduction in ionized calcium with secondary hyperparathyroidism and resultant bone loss. Chronic fluoride exposure may also cause endoplasmic reticulum (ER) stress which predisposes to obesity, diabetes, insulin resistance, hypertension, atherosclerosis and cardiovascular disease [8].

Five subjects were noted to have vitamin D deficiency. Calcium and phosphate levels were normal in all subjects. Elevated alkaline phosphatase was noted in most patients. Fluoride is an abundant geological mineral ion that is easily absorbed from the stomach and small intestine. It is readily deposited in calcified tissues, and being similar in size to the hydroxyl ion, it gets incorporated as fluoro-apatite. The resulting crystal lattice is more compact, less soluble, and more stable than hydroxyapatite. Moreover, fluoride is an anabolic agent that uncouples bone remodeling and causes increased bone formation by the osteoblasts. This also causes skeletal accretion and increased bone density [15]. These are apparent on the skeletal radiology as diffuse sclerosis and on the DXA derived parameters that demonstrate sclerotic BMD T-scores and a high trabecular bone score.

It is essential to ensure adequate calcium and vitamin D supplements to all individuals as this might mitigate fluoride toxicity. Although there are studies evaluating various treatment modality such as vitamin C, methionine with vitamin E in skeletal fluorosis, prevention appears to be the only effective strategy in this condition. Provision of safe drinking water, betterment of the living conditions of individuals and education regarding the potential harmful effects of drinking fluoride-contaminated water will probably help in reducing the prevalence of endemic fluorosis.

This is the first study that comprehensively describes the bone health in subjects with skeletal fluorosis although it is limited by the small sample size and non-availability of biochemical markers of bone turnover. The diagnosis of fluorosis was further established by the elevated levels of urine fluoride in affected subjects. Fluorosis related low bone mass may not be apparent at central sites such as the hip and spine in which case the distal third of forearm may be utilized to assess decline in bone mineral density.

5. Conclusion

While fluorosis continues to be a challenge in endemic regions, the presence of osteomalacia proves to be a treatable component of the disease condition. The complications of the disease might be mitigated if

diagnosed early and steps are taken to prevent intake of excess fluoride through provision of safe drinking water, promote adequate calcium nutrition, improving the living standards of individuals and education regarding the harmful effects of continued consumption of fluoride contaminated water.

Declaration of conflict of interest

All authors declare that they have no conflict of interest.

Funding declaration

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Consent

Written informed consent was obtained from the patient prior to submission of this manuscript.

Declaration of competing interest

The authors declare that there is no conflict of interests.

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