AN EPIDEMIOLOGICAL, CLINICAL AND BIOCHEMICAL STUDY OF ENDEMIC, DENTAL AND SKELETAL FLUOROSIS IN PUNJAB

by

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Since 1958 the Department of Medicine, Patiala, has been actively engaged in epidemiological, clinical and biochemical studies of endemic fluorosis in Punjab, one of the most highly endemic areas in the world. Extensive data on dental, skeletal and neurological aspects of fluorosis have been fully reported in our earlier studies (1-5). The object of the present communication is to evaluate the role of various factors associated with F toxicity. Even where F levels in the water are identical, variations in the incidence of F intoxication clearly point to the existence of causative factors in addition to fluoride.

Material and Methods

An epidemiological survey to determine the incidence of dental fluorosis was carried out in 358 villages of Punjab. Children between 5 to 17 years of age were examined for dental mottling and characteristic dental pigmentation.

Besides the above dental survey, ten villages from the endemic fluorotic area of Punjab each with a different F concentration in drinking water were selected to assess the effect of various factors in F intoxication. Children and adults (both males and females) in these villages were subjected to thorough clinical and radiological examination. Interosseous membrane calcification had been taken as a definite index of skeletal fluorosis.

The waters of the ten villages were analyzed for various important chemical constituents such as total hardness, calcium and magnesium hardness and alkalinity. In an Indian village there is no central water supply. Almost each house has its own hand pump. The F concentration at these pumps shows a wide variation in the same village because of the different depths of the wells. Moreover, the farmers and laborers (the subject of this study) work in the fields. They imbibe water from the places wherever they are during the day. It is, therefore, not possible to evaluate precisely the incidence of fluorosis according to a particular F concentration in the sample of water. However, the mean F concentration of all water samples has been computed for the purpose of determining the incidence of fluorosis.

Dental Fluorosis

About 46,000 children were examined in 358 Punjab villages. The incidence of dental involvement as correlated with fluoride concentration is tabulated in Table I.

From the Government Medical College, Patiala, India

TABLE I

Number of Villages	Maximum F Concentration in Water (ppm)	Incidence of Dental Mottling
210	1.4	0 - 10%
96	2.3	10 - 30%
52	Above 2.3	Above 30%

The incidence of dental fluorosis rises with increasing F concentration but no linear relationship between F levels in water and the incidence of dental involvement is noted. In the ten villages selected for the special study, the incidence of dental mottling in children and adults is given in Table 2.

TABLE 2

Incidence of Mottling in Ten Villages

Name of the Village	Fluoride Concentration (ppm)	Incidence of Dental Mottling in Children (Percent)	Incidence of Dental Mottling in Adults (Percent)
Gharachaon	1.4	22.6 (124)	13.8 (87)
Laluwala	2.4	30.6 (49)	60.2 (74)
Dharpai	3.0	24.5 (57)	47.6 (107)
Bhodipura	3.0	55.9 (34)	31.2 (64)
Rajthal	3.3	47.0 (133)	10.0 (160)
Bhikki	3.3	53.4 (146)	52.5 (160)
Sanghera	3.6	27.4 (317)	49.4 (154)
Ramuana	5.0	52.7 (93)	56.6 (90)
Gangigulabsingh	8.5	81.4 (43)	55.6 (58)
Kahara	9.7	66.0 (50)	70.7 (232)

(Figures in parenthesis denote the number of cases examined.)

The incidence of dental fluorosis in a locality with mean F concentration of 1.4 ppm was about 22.6%. Comparison of this percentage with that in Table I shows that it is impossible to attribute the incidence of dental fluorosis solely to the F content of drinking water.

Skeletal Fluorosis

During the epidemiological survey of the villages of Punjab, we examined 1065 cases of skeletal fluorosis, the largest series ever reported. In addition, detailed examinations were carried out on cases which were admitted to the hospital from time to time during the last 10 years. Table 3 gives the overall results of this survey.

TABLE 3

Results of Survey

			Males	Females
Skeletal fluorosis detected by x-ray: 1,065				
Latent with symptoms or	835	80.3%		
without symptoms:	210	19.7%		
Without crippling:	624	58.6%	70%	30%
With crippling deformities:	142	13.3%	92%	8%
With neurological complications:	89	8.4%	94%	6%

Whereas dental fluorosis is easily recognized, the incipient skeletal involvement is not clinically obvious until the disease has advanced to the state of crippling. However, radiological changes are discernable in the skeleton much earlier and provide the only means of diagnosing the disease in its early and relatively asymptomatic stage. These cases are usually young adults whose only complaints are vague pains most frequently in the small joints of the hands and feet, the joints of knee and spine. Such cases are common in an endemic area. They are misdiagnosed as rheumatoid arthritis or ankylosing spondylitis. In the more advanced stages, there is an obvious stiffness of the spine with limitation of its movements followed by kyphosis. Patients experience difficulty in walking, partly because of stiffness and limitation of movements of various joints and partly because of neurological defects in the advanced cases.

The skeletal changes in endemic fluorosis are best described under the following headings:

Gross Changes in Skeleton

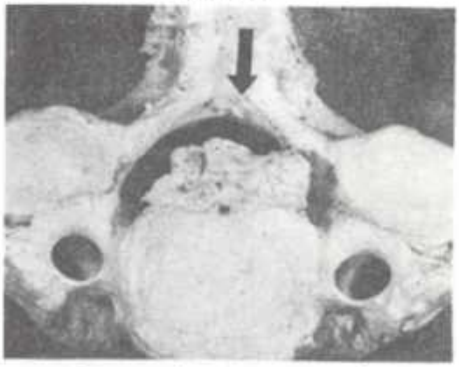
The gross skeletal changes in cases of endemic fluorosis are quite distinctive and characteristic. They have been described in detail in our earlier publications (4).

We had the unique opportunity to study the complete macerated skeleton of a person affected by endemic fluorosis. The bones were heavy and irregular, their dull color was due to irregular deposition of F. The sites of muscular and tendonous insertions were rendered abnormally prominent by excessive periosteal reaction with development of multiple exostoses. Irregular bone was laid down along the attachment of muscles and tendons in the extremities as well as in joint capsules and in interosseous membranes. The latter is particularly helpful as a diagnostic feature in borderline cases where the density of the bone is not markedly increased. Maximum changes were detected in the spine, particularly in the cervical region. The vertebrae showed altered proportions and measurements in all planes, but the most striking abnormality was the gross reduction of the antero-posterior diameter of the spinal canal, which in the case studied at autopsy was reduced to 2 mm at the level of third and

Fig. 1

Dental Fluorosis in Endemic Area. Note Characteristic Pigmentation of teeth.

Fig. 2



Third Cervical Vertebra in Fluorosis. Huge Exostosis Projecting into Spinal Canal.

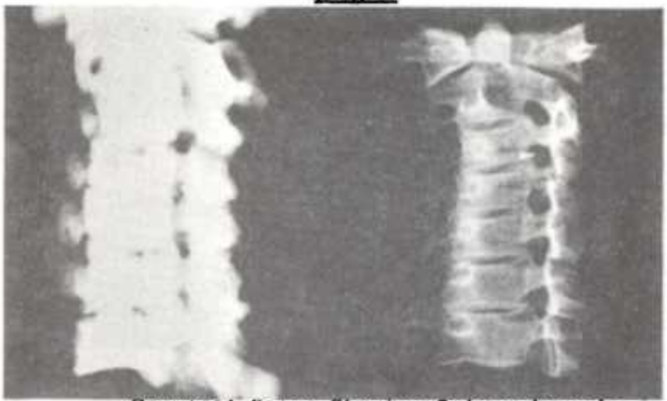
fourth cervical vertebrae (Fig. 2). Since the average antero-posterior diameter of the spinal cord in the cervical enlargement is about 8 mm and the bulge of the ligamentum flavum has also to be accomodated, compression of the cord is almost inevitable. The vertebrae were fused in many places, which explained the marked limitation of movement and the resemblance of the disease to spondylitis ankylopoietica. The intervertebral foramina were narrowed and irregular, which accounts for radicular manifestations. In the skull there were no conspicuous changes, but the margins of the foramen magnum were irregular and its diameter reduced as a result of deposition of new bone. The other small foramina were not significantly affected. Therefore, there was no cranial nerve involvement.

The irregular bone deposition was obvious clinically in a large percentage of cases as bony excrecences of varying size. They were noted near the knee joints, along the anterior border of the tibia and near the olecranon. The skeletal changes resulted in limitation of movement, particularly of the cervical and lumbodorsal spine and the joints of the lower extremities. The crippling deformities were due partly to muscular dysfunction and partly to immobilization necessitated by pain.

Radiological Changes

The most pronounced radiological changes were seen in the vertebral column, particularly in the cervical region (Fig. 3). Osteosclerosis and irregular osteophyte formation were noted in the vertebral body, the transverse and spinous processes and in the pedicles and laminae. Beak-like lipping and a chalky white ground-glass appearance of the entire vertebral column were the characteristic radiological features, along with calcifications of the intervertebral ligaments (Fig. 4). As a result of the irregular exostoses, there was encroachment on the intervertebral foramina and the spinal canal. Next to the spine, osteosclerosis was most evident in the pelvis, along with calcification of sacro-tuberous and sacro-spinous ligaments.

Fig. 3



Cervical Spine Showing Osteosclerosis and Narrowing of Intervertebral Foraminae as Compared to Normal Cervical Spine

Fig. 4

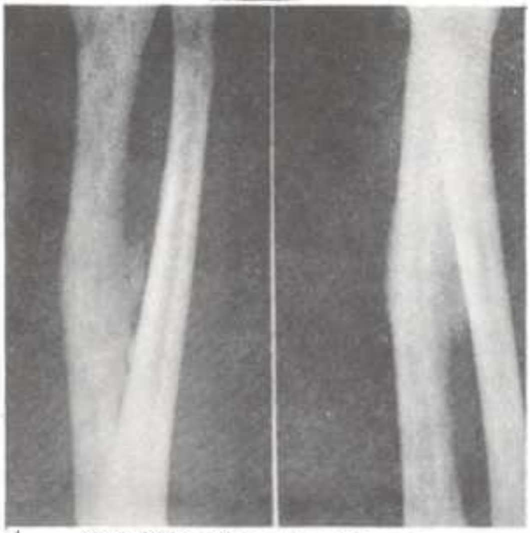
Skiagram of the Lumbar Spine; Osteosclerosis and Osteophytosis.

Irregular periosteal bone formation was observed along the tendons and the fascial and muscular attachments, including the interosseous membranes of forearms and legs (Fig. 5), linea aspera, the deltoid tuberosity, the lower margins of the ribs, the attachment of the Achilles tendon, the tibial tubercles and the greater trochanter. Chest x-rays revealed a peculiar contrast of the marble white, bony cage with the radiolucent lungs. The changes in the skull were not striking, although there was thickening of the vault with sclerosis near the suture lines. The sella turcica and the nasal sinuses were normal and there was no significant narrowing of the basal foramina.

Histopathology

Bone biopsy was obtained from the tibia or iliac crest in 21 cases and in one autopsy. In general, the compact bone showed disordered lamellar orientation and an enlarged, poorly formed Haversian system resembling the changes described in experimental animals. In the spongy bone, areas of osteoid tissue were found among well formed trabeculae. Some of the irregular deposits of osteoid tissue extended into the attached muscles. The bone trabeculae were very dense in places and contained a considerable amount of calcium. The areas around the vascular spaces stained deeply with eosin. In two additional cases tissue procured at biopsy consisted of calcified muscular attachment. It showed skeletal muscle infiltrated with areas of irregular calcification. Several trabeculae of osteoid tissue and occasional bony trabeculae were also seen.

Fig. 5



Calcification of Interosseous Membrane, a Characteristic Radiological Feature Helpful for Diagnosis.

Chemical Composition

In 20 patients fluoride content of the bone tissue ranged from 700 to 7000 ppm dry weight compared with a "normal" of 1100 $\pm$ 200 ppm in a person from a non-fluorotic area.

Deformities and Crippling Fluorosis

In addition to high fluoride water, other sources of F ingestion in the area surveyed by us were vegetables grown in the fluorotic soil and food processed in water contaminated with F. Therefore, it was not surprising that we encountered 142 cases of crippling fluorosis.

Crippling is due partly to mechanical factors and partly to immobilization necessitated by pain and paraplegia. The most common deformities are kyphosis, flexion deformity of hips, flexion deformity of the knee and fixation of chest in position of inspiration due to calcification of cartilages. The picture of advanced crippling fluorosis was strikingly uniform (Fig. 6 and 7). The quadriplegic patient provided a grim picture of the ravages of the disease bent with kyphosis, with markedly restricted movements of his spine, contractures and flexion deformity of hips and knees. The chest was usually fixed, with minimal expansion. Due to the extreme fixation of the spine the body moved as a single unit when an attempt was made to straighten any portion of it.

Fig. 6

Fig. 7

Kyphotic Deformity and Invalidism in Advanced Fluorosis

In ten villages with varying fluoride concentration the incidence of skeletal fluorosis was correlated with the water's F concentration (Table 4).

TABLE 4

Incidence of Skeletal Fluorosis

Name of Village	Concentration of Fluoride in Water (ppm)	Incidence of Skeletal Fluorosis (%)	Crippling Fluorosis
Gharachon	1.4 (0.9-2.5)	2.4 (82)*	-
Laluwala	2.4 (1.0-5.5)	23.0 (74)	-
Dhapai	3.0 (1.1-5.5)	19.6 (107)	-
Bhodipura	3.0 (1.3-5.2)	42.2 (64)	+
Rajthal	3.3 (0.5-6.5)	10.0 (160)	-
Bhikhi	3.3 (1.0-5.9)	45.6 (160)	+
Sanghera	3.6 (1.1-5.8)	33.1 (154)	+
Ramuana	5.0 (1.5-11.5)	60.0 (90)	+
Ganjigulab Singh	8.5 (3.7-14.0)	58.9 (56)	+
Khara	9.7 (6.0-16.2)	70.7 (232)	+

*Figures in brackets denote the total number examined.

At a mean concentration of 1.4 ppm F, the incidence is practically nil. It rises with increasing F concentration in water. However, like in dental fluorosis, the concentration of F is not solely responsible for the incidence of skeletal fluorosis.

Table 4 illustrates two interesting observations. Cases of crippling fluorosis do occur in endemic proportion where the mean fluoride content of water is as low as 3 ppm.

Whereas we encountered crippling fluorosis in some villages with a mean F concentration of 3 ppm, the same concentration did not cause crippling in two others. Therefore, factors other than fluoride must have a modifying role upon the disease.

Neurological Complications of Fluorosis

According to our earlier studies some cases of skeletal fluorosis exhibit neurological complications of radiculomyelopathy due to compression of the spinal cord and roots because of irregular bone deposits in and around the spinal canal. This was convincingly demonstrated by us in a macerated skeleton (4). So far we have studied in detail 62 proven cases of skeletal fluorosis with neurological manifestations, the largest series in the world. The details of neurological manifestations are to be presented elsewhere. A summary is shown in Table 5.

TABLE 5

Neurological Manifestations in 57 Cases

Lesions	Males	Females
Cervical radiculomyelopathy	31	-
Cervical radiculomyelopathy with deafness	1	-
Cervical radiculomyelopathy with cerebellar involvement	1	-
Cervical myelopathy (uncomplicated)	4	1
Cervicdorsal myelopathy	2	1
Dorsal myelopathy	12	3
Cervical radiculopathy	1	-
Peripheral neuritic type	3	-
Fluorosis associated with cerebrovascular accidents	2	-
Total	57	5

Vertebral artery is compressed as it passes through the cervical spine.

An additional 27 cases were detected at the time of surveys but have not been studied thoroughly by hospitalization. Therefore they are not included here.

Factors Influencing Toxicity

1. Fluoride Content of Drinking Water: It is universally agreed that fluoride ingestion produces toxic effects, but the concentration which may produce deleterious effects is the subject of controversy. The minimal threshold has not yet been established definitely. In some studies from India, very low F concentrations have been shown to be associated with marked fluorosis. According to our extensive survey of villages an F concentration of 0.9 ppm to 2.5 ppm is associated with an incidence of only 2.4% with a range of 1.3 to 5.2 ppm F in water. The incidence of skeletal fluorosis is not solely dependent on the F concentration of water. Upon comparing the two villages, Rajthal and Bhikhi, with practically the same mean F level of 3.3 ppm, a marked difference in the incidence of skeletal fluorosis is noted, namely 10% and 45.6% respectively. In Bhikhi, a large number of crippling fluorosis cases were observed, whereas not a single similar case was detected in Rajthal. This wide discrepancy clearly points to the existence of factors in addition to the F concentration in water.

2. Duration of Fluoride Exposure: The duration of F consumption influences the development of endemic fluorosis. In villages with a similar F concentration the incidence was found to increase with age. In those with a lower F concentration, skeletal fluorosis is detected in the higher age group whereas where high F water is imbibed it is encountered at a younger age.

TABLE 6

Relationship of Fluoride Levels to Other Constituents of Water (ppm)

Village (Mean)	Fluoride	Total Hard-ness	Ca Hard-ness	Mg Hard-ness	Alka-linity	Chlo-ride
Normal	0.28	287	96	13	27	46
Gharachon	1.4	235	71	191	588	129
Laluwala	2.4	116	48	708	798	143
Dhapai	3	357	108	268	753	265
Bhodipura	3	287	73	205	488	27
Raithal	3.3	601	358	344	519	409
Bhikhi	3.3	136	56	80	300	87
Sangher	3.6	237	81	185	460	107
Ramuwala	5.0	101	27	62	869	54
Ganjigulab/ Singh	8.5	30	14	17	851	53
Khara	8.5	30	14	17	851	53

3. Sex and Occupation: These factors also influence the development of endemic fluorosis, particularly in relationship to severe complications of neurological and crippling fluorosis. There were only 5 females compared to 57 males with neurological fluorosis in the hospitalized cases. The disease is far more common in laborers and farmers who have to do hard manual work and carry heavy loads on the head. This factor may account for the higher incidence of neurological (Table 5) and crippling fluorosis in men than in women.

Another contributory factor could be the fact that women migrate to another village after their marriage where the F content of the water supply is different.

4. Chemical Composition of the Water: Besides F in water a number of other constituents are also important especially calcium and magnesium hardness and alkalinity. We showed that F concentration bears an inverse relationship to total hardness and calcium hardness (8). In areas with little F in water, we found high hardness values. That the incidence of endemic fluorosis is dependent to a great extent upon the hardness of water is illustrated by comparing the analyses of water constituents from the village of Bhikhi and Rajthal (Table 6).

These two villages with the same mean F content show a wide variation in incidence of endemic fluorosis. Other variants such as the nutritional status, climate, duration of fluoride exposure, sex, profession etc. were identical in the two villages. Hardness of water was the only difference. In the U.S.A. most water containing fluoride is hard water and the fluoride/hardness ratio is greater than 1 in 500. In our study the fluoride/hardness ratio was much less as shown in Table 7.

TABLE 7

Relation Between Fluoride and Other Constituents of Water

Name of	F: Total Hardness	F: Ca Hardness	F: Alka-linity	Ca: Alka-linity
Normal	1:1025	1:340	1:97	1:2.8
Gharachaon	1:167.8	1:51	1:420	1:8.2
Laluwala	1:48	1:20	1:332	1:16.6
Dharpai	1:125	1:36	1:251	1:6.9
Bhodipura	1:96	1:24	1:162	1:6.6
Raithal	1:182	1:108	1:159	1:1.4
Bhikki	1:41	1:17	1:91	1:6.4
Sanghera	1:66	1:22	1:128	1:5.6
Ranuana	1:20	1:5	1:194	1:32.1
Gangigulab/ Singh	1:4	1:2	1:101	1:60.7
Khara	1:10	1:3	1:40	1:11.5

Both Calcium and magnesium content of water have a protective influence regarding the absorption of F and its subsequent deposition in the skeleton (9). In India, lower toxic levels of F may therefore be related to lesser hardness of water as shown in the analysis of water constituents in some of the endemic areas.

5. Nutritional Factors: Some believe that the high incidence of endemic fluorosis in India is partly related to malnutrition. Our studies in Punjab did not bear out this theory. Punjab is one of the best nourished states in India and yet this very state shows the highest incidence of fluorosis. It has recently been shown by calcium balance studies (10) that the cases of fluorosis retain greater amounts of calcium and that increased retention is due to lower excretion in urine and faeces.

6. Climatic and Geological Factors: Endemic fluorosis has been observed only in those areas where the soil is sandy and the climate is hot and dry. The average temperature during the summer is above 100°F. Rainfall is rather scanty. Moreover fluorosis occurred only in villages with superficial subsoil water. The deep wells showed less F in water. This observation has been utilized in the prevention of the disease.

7. Fluoride from Food and Beverages: Besides F imbibed in drinking water considerable quantities of F may be ingested with food grown in F rich soil and with tea and wines (11). Recently high levels of fluoride have been shown to be present in the Punjab cooking salt and in turmeric which is used as an adjuvant in cooking throughout India. We have not as yet precisely evaluated these factors in our endemic area. They may be significant since the Punjab villager consumes much tea and alcoholic drinks.

<u>Bibliography</u>

1. Singh, A. and Jolly, S.S.: Quarterly J. Med. N.S. 30:357, 1961.
2. Singh, A., Jolly, S.S. and Bansal, B.C.: Lancet 1:197, 1961.
3. Singh, A., Vazirani, S.J., Jolly, S.S. and Bansal, B.C.: Post-Grad. Med. Jour. 38:150, 1962.
4. Singh, A., Dass, R., Hayreh, S.S. and Jolly, S.S.: J. Bone and Joint Surgery 44B:806, 1962.
5. Singh, A., Jolly, S.S., Bansal, B.C. and Mathur, O.C.: Medicine 42:299, 1963.
6. Mathur, O.C., Singh, I.D., Singh, K. and Singh, A.: Ind. J. Physiology and Pharmacology 7:6, 1962.
7. Saini, A.S., Singh, I.D., Bajaj, B.R. and Singh, A.: Ind. Jour. Med. Res. 52:2, 1964.
8. Singh, A., Singh, B.M., Singh, I.D., Jolly, S.S. and Malhotra, K.C.: Ind. Jour. Med. Res. 54:591, 1966.
9. Marier, J.R., Rose, D. and Boulet, M.: Arch. Environ. Health 6:664, 1963.
10. Srikantia, S.G. and Siddiqui, A.H.: Clin. Sci. 28:477, 1965.
11. Soriano, M. and Manchon, F.: Radiology 87:1089, 1966.