Research Article

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Thoracic Ossification of Ligamentum Flavum Caused By Skeletal Fluorosis: Breaking the Etiopathological Barrier -Answer to the Crippling Disease of the Society

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Abstract

Background: *Thoracic ossification of ligamentum flavum (OLF) caused by skeletal fluorosis is rare [1]. Only six patients had been reported in the English literature. This study is the second study to the best of our knowledge in literature.*

Aims and Objectives: *To evaluate the causation of ossification of ligamentum flavum due to fluorosis in accordance with reports from the first clinical series of this disease. Exact etiopathogenesis of thoracic ossification of yellow ligament is not known and causation due to fluorosis is rare, so this study was hypothesized [2].*

Materials and Methods: *This is a prospective study of patients with thoracic OLF due to skeletal fluorosis who underwent surgical management at the NIMS hospital between 2017 and 2018. A total of 16 cases were enrolled, (56.25%), 9 males and 7 (43.75%) females, age ranging from 37 to 62 years (mean 50.5 years). Imaging showed OLF together with ossification of interosseous membranes, including interosseous membranes of the forearm (14/16 patients 87.5%).Urinalysis showed a markedly high urinary fluoride level in 15 of 16 patients (93.75%).Ossified ligamentum flavum sent for estimation of fluoride levels in 16 patients showed high fluoride level in the bone ash prepared from the oyl in 15 patients and other structures sent as control were ,spinous process ,interspinous ligaments didn't show any fluoride deposition.*

Results: *Out of 16 patient 15 patient had fluoride levels more than 6000mg/kg, 7 patient had values between 6,000 – 7,000 mg/kg, 5 patient had values between 7,500 – 9,000 mg/kg and 3 patients had values > 8400 mg/kg. Controls were sent as spinous processes had normal fluoride level between 500-1000 mg/kg and interspinous ligaments sent showed no fluoride levels. Out of 16 patients 9 patients had multiple level dorsal OYL both contiguous and non-contiguous, contiguous in 4 patients and non – contiguous in 5 patients.7 patients had single level dorsal OYL.*

Most common segment involved in OYL is T9 and D10 level in 14 patients. Sato classification 6 were Type A, 5 were Type B, 3 were Type C, 2 were Type D

Conclusion: *This is the largest series of ossification of dorsal yellow ligament due to fluorosis. And consideration of fluorosis as one of the important etiological cause for OYL to be kept in mind and all patients with OYL to be screened for Fluorosis and this would also help as a preventive measure for the people around the surroundings of the affected person and would help the society from a crippling disability.*

Keywords: Ossification of Ligamentum Flavum, Thoracic Spinal Stenosis, Skeletal Fluorosis

Introduction

Thoracic spinal stenosis, in contrast to stenosis of the cervical and lumbar spine, is rare. The condition may be congenital or acquired. Congenital thoracic spinal stenosis resulting in myelopathy has been demonstrated to a limited extent in patients with skeletal disorders [3].

Acquired thoracic spinal canal stenosis related to disc degeneration, osteophytes, or hypertrophy of the posterior spinal elements has been reported in numerous case reports and clinical series Of the posterior spinal elements that might be implicated in acquired thoracic spinal canal stenosis, ossification of the ligamentum flavum (OLF) has been suggested as the most common contributing factor [4].

Typical clinical features of fluoride intoxication include dental fluorosis, diffuse densification of bone, and calcification of bony insertions of many ligaments, discs, and interosseous membranes (i.e., interosseous membranes of the ribs, forearm, and leg; posterior longitudinal ligament; transverse atlantal ligament; ligamentum flavum; and membrana obturatoria) [2-3,5-6]. Rarely, skeletal fluorosis may cause thoracic OLF; six cases have been reported in the English literature. No large-sample clinical series of such cases has been reported in the English literature.

The purpose of this study was to break the etiological barrier and find out the cause for thoracic ossification of ligamentum flavum at our institute and what is the relation to fluorosis.

Aim of the Study

To evaluate the cause of thoracic ossified ligamentum flavum and association with fluorosis.

Materials and Methods

This is a prospective study of patients with thoracic OLF due to skeletal fluorosis who underwent surgical management at the NIMS hospital between 2017 and 2018. Diagnosis of skeletal fluorosis was made based on the epidemic history, clinical symptoms, radiographic findings, and urinalysis. Laminectomy decompression of the involved thoracic levels was performed in all cases.

Diagnosis of Fluorosis

Urinary fluoride levels are the best indicators of fluoride intake. Since, fluoride excretion is not constant throughout the day, 24-hour samples of urine are more reliable than random or morning samples for the estimation of fluoride content [7,8]. All patients underwent 24-hour urinary fluoride levels estimation. The urinary fluoride estimation was done by Ion Selective Electrode method using Orion 4 star Ph/ISE bench top meter equipment and a value > 1.6 mg/L was diagnostic of fluorosis [9]. X-ray A-P view of the forearm was done in patients for the ossification of interosseous membrane.

Figure 1: X ray of the forearm showing ossification of the interosseous membrane

Figure 2: Instrument used for estimation of the 24 hour urinary fluoride levels by Ion –selective electrode method

All 16 patients underwent surgery and Ossified ligamentum flavum sent for estimation of fluoride levels in all patients .As a control group spinous process and interspinous ligaments were sent for estimation of fluoride levels.

The samples are prepared for analysis by ashing at 550 degrees C, dissolving in HNO3 (4 mol/1) and adjusting the pH with NaOH (4 mol/1) and Total Ion Strength Adjustment Buffer, Absolute values are derived from a calibration curve based on aqueous NaF-buffer solutions. The calibration curve is linear in the range 5.2-10(-3)-1.0-10(-5) mol/1F-. The minimum limit of measurement is 5.2 X 10(-6) mol/1F-. The method has an accuracy of 96.1 % or 92.3% with a series precision based on the Pearson variability coefficient of 1.68%. The normal mass fraction of fluoride in human bones was found to be between 500 and 1000 - 10(-6) F-/ash.

Statistical Methods

Descriptive and inferential statistical analysis was performed. Results on continuous measurements were presented as Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). The significance was assessed at 5 % level of significance.

Analysis of variance (ANOVA) was used to find the significance of study parameters of patients, Chi-square/ Fisher Exact test was used to find the significance of study parameters on a categorical scale between two or more groups.

Results

A total of 16 cases were enrolled, (56.25%), 9 males and 7 (43.75%) females, age ranging from 37 to 62 years (mean 50.5 years).

Imaging showed OLF together with ossification of interosseous membranes, including interosseous membranes of the forearm (14/16 patients 87.5%).

Urinalysis showed a markedly high urinary fluoride level in 15 of 16 patients (93.75%).

All the patients were operated and OYL was sent to National institute of nutrition, Hyderabad for the estimation of Fluoride levels. Along with the OYL, spinous process, interspinous ligaments were also sent for estimation of the fluoride levels.
The OYL sent was prepared into bone ash and fluoride levels were estimated.
All patients with ash concentration more than 6000 mg/kg were considered as Fluorosis.

Out of 16 patient 15 patient had fluoride levels more than 6000mg/kg, 7 patient had values between 6,000 – 7,000 mg/kg, 5 patient had values between 7,500 – 9,000 mg/kg and 3 patients had values > 8400 mg/kg.

Controls sent spinous processes had normal fluoride level between 500-1000 mg/kg and interspinous ligaments sent showed no fluoride levels.

Out of 16 patients 9 patients had multiple level dorsal OYL both contiguous and non-contiguous, contiguous in 4 patients and non – contiguous in 5 patients.7 patients had single level dorsal OYL.

Most common segment involved in OYL is T9 and D10 level in 14 patients.

All the patients are followed up for a period of 6 months and all had relief of spasticity and none of the patients developed kyphotic deformities.

Table 1: Showing the characteristics of patients, level of involvement, level of decompression and CT grade (sato) of OYL

Case no	Age/sex	Level of OYL	Level of decompression	CT GRADE OF OYL(Sato)
1	M	T5-T6,T8-T10	T5,T6,T8,9,10	A
2	M	T9-T12	T9-T12	B
3	M	T2-T5,T8-T9	T2-T5,T8-T9	A
4	F	T9-T10	T9,T10	B
5	M	T7-T12	T7,8,9,10,11,12	D
6	F	T11-12	T11,T12	B
7	M	T4-T7,T9-T11	T4-T7,T9-T11	A
8	M	T5-T6	T5,T6	C
9	F	T8-T9	T8,T9	D
10	F	T9-T10	T9-T10	B
11	F	T4-T5	T4,T5	C
12	M	T3-T6,T9-11	T3-T6,T9-T11	A
13	F	T2-T3	T2,T3	C
14	M	T9-T10	T9,T10	A
15	F	T8-T12	T8-T12	B
16	M	T2-T4,T7-T9	T2-T4,T7,8,9	A

Sato classification 6 were Type A, 5 were Type B, 3 were Type C, 2 were Type D

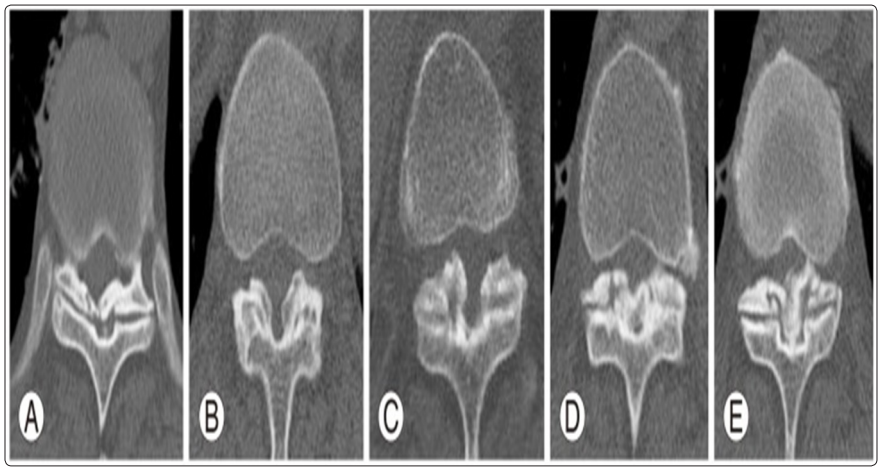

Figure 3: Sato classification according to the progression of the ligament ossification
(A) Lateral type which means ossification of only the capsular portion of the ligamentum flavum.
(B) Extended type which means extended ossification of the interlaminar portion.
(C) Enlarged type which means anteromedial thickening and enlargement of ossification.
(D) Fused type which means fusion of the bilateral ossified masses at the midline.
(E) Tuberous type which means anterior growth of the fused mass of ossification.

Table 2: Table showing normal levels of Fluoride in bone ash preparation

Diagnosing Skeletal Fluorosis: Us Public Health Service Chart

US Public Health Service 2016	
OSTEOSCLEROTIC PHASE	**ASH CONCENTRATION (mg/kg)**
Normal Bone	500 – 1,000
Preclinical Phase	3,500 – 5,500
Asymptomatic; slight radiographically-detectable increases in bone mass	
Clinical Phase I	6,000 – 7,000
Sporadic pain; stiffness of joints; osteosclerosis of pelvis & vertebral column	
Clinical Phase II	7,500 – 9,000
Chronic joint pain; arthritic symptoms; slight calcification of ligaments; increased osteosclerosis/ cancellous bones; with/without osteoporosis of long bones	
Phase III: Crippling Fluorosis	> 8,400
Limitation of joint movement; calcification of ligaments/neck, vert. column; crippling deformities/spine & major joints; muscle wasting; neurological defects/compression of spinal cord	

So in our results Fluorosis is considered as one of the most important cause for development of Ossified ligamentum flavum.

Discussion

Thoracic OLF was first reported by Polgar in 1920 based on lateral radiographs [10]. Since then, hundreds of cases of thoracic OLF have been reported from several clinical series and numerous case reports. However the etiology of OLF is unclear. As most OLF cases had involved T9 and T12, Barnett et al. suggested that hypermobility of the lower thoracic spine might promote degeneration and canal stenosis.

Liao found high prevalence of anterior osteophytes co-occurring with herniated intervertebral disc at the symptomatic OLF segments and concluded that OLF might be a degenerative response to micro injury of the ligamentum flavum [8]. This hypothesis is histologically supported by Okada and colleagues who found that OLF formed in the hypertrophic ligamentum flavum with fibrocartilage proliferation [11]. This was thought to be a form of mechanical injury; therefore, it was theorized that OLF might develop secondary to the specific fiber reconstruction of the ligamentum flavum in response to mechanical stress.

However, Muthukumar recently reported two cases of OLF caused by fluorosis, and Wang et al. reported that fluorosis could cause ossification of numerous ligaments. These reports provide evidence that fluorosis could play a role in OLF [12-14].

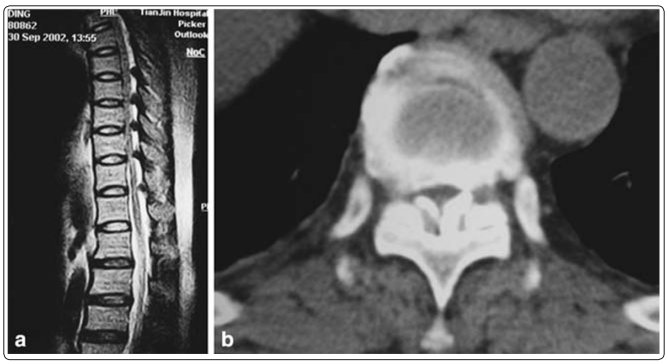

Figure 4: (a) T2 weight MRI of thoracic spine showed continuous multi-level ossification of ligamentum flavum between T7 and T12 (case 5). (b) CT scan showed ossified ligamentum flavum, note that there was a thin gap between the ossified ligament and the lamina

The pathogenesis of ossification of the ligaments in OLF remains speculative. High expression of transforming growth factor beta-1 (TGF-b1) by fibroblasts was found in the ossified matrix within ossified ligaments and in chondrocytes within cartilaginous areas adjacent to the ossified ligaments [26]. TGF-b1 may play a role in chondroid metaplasia and ectopic ossification in OLF. Recent experimental evidence suggests the involvement of proto-oncogenes c-fos and c-jun in skeletal fluorosis activation and proliferation of osteoblast-like cells, enhancing expression of messenger ribonucleic acid and c-fos and c-jun proteins.

All patients in our series had the characteristic features of fluorosis, including diffuse densification of bone and ossification of interosseous membranes [13-14]. Second, a larger number of spinal segments were involved. In Shiokawa's series [15], OLF was located between T9 and T12 in 27 of 31 patients (87%); in only 4 patients was OLF located outside of this range. In two patients coexistent OLF was also located between T9 and T12.

In our study Out of 16 patients 9 patients had multiple level dorsal OYL both contiguous and non-contiguous, contiguous in 4 patients and non –contiguous in 5 patients.7 patients had single level dorsal OYL. Most common segment involved in OYL is T9 and D10 level in 14 patients.

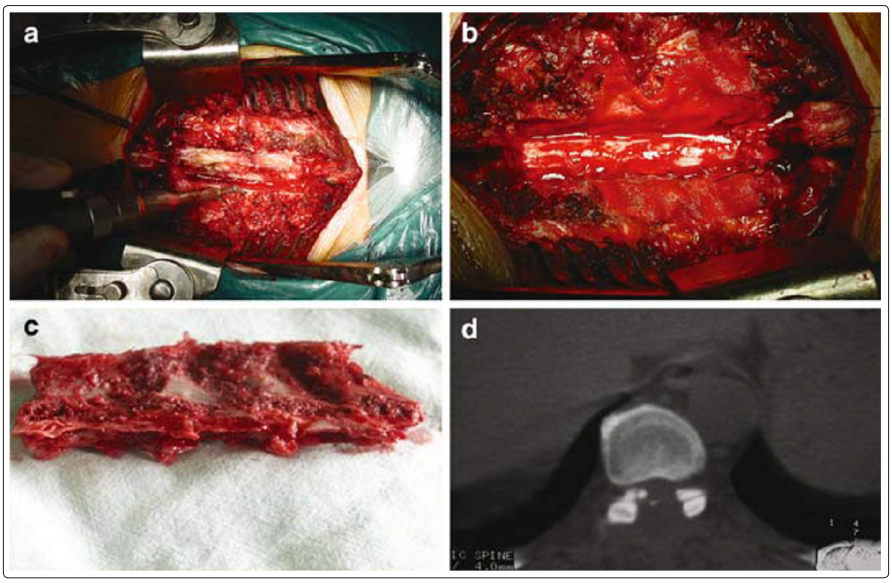

Figure 5:
(a) Operation picture showed en bloc method for laminectomy with a high speed drill.
(b) Inter operation picture showed the dura mater was totally decompressed.
(c) The en bloc removed lamina, note the nodular ossified ligamentum flavum.
(d) Postoperative CT scan showed sufficient decompression, note the lateral two thirds of the facet joint was preserved and the ossified dura mater was partly left.

Conclusion

Fluorosis can cause ossification of the thoracic ligamentum flavum, as well as other ligaments. Comparing with other OLF series, a larger number of spinal segments were involved. In this patient series, skeletal fluorosis was diagnosed based on epidemic history, clinical symptoms, medical imaging, and urinalysis.

This is the largest series of ossification of dorsal yellow ligament due to fluorosis.
And consideration of fluorosis as one of the important etiological cause for OYL to be kept in mind and all patients with OYL to be screened for Fluorosis and this would also help as a preventive measure for the people around the surroundings of the affected person and would help the society from a crippling disability [1-30].

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