

MRI CHANGES IN COMPRESSIVE MYELOPATHY IN FLUOROSIS- STUDY OF 18 CASES FROM NORTH WEST INDIA

Ashok Panagariya, Ravindra Singh, Paresh Sukhani, Bhawana Sharma

Department of Neurology, SMS Medical College, Jaipur, Rajasthan, India

Abstract : This study was carried out to highlight the spectrum of magnetic resonance imaging changes in fluorotic spine, its frequent occurrence as cause of cord compression in this part of country and to correlate the radiological changes with the duration and severity of neurological deficit. 18 patients with clinically and biochemically proved fluorosis had MRI of whole spine on 1.5 tesla super conducting magnet between Jan 2002-Jan 2004. Clinical manifestations included pain and stiffness in spine, motor weakness, radicular pain, numbness and tingling sensation of limbs and retention of urine. Cord compression was seen in all patients. Thickening of PLL was seen in 14 patients out of which 7 patients showed ossification. Thickening of Ligamentum Flavum was seen in 16 patients, 11 of them showed ossification, intramedullary hyperintense signals representing cord edema was noted in 17, neural compression in 9 and target sign in 2 patients. There was a direct correlation between neurological deficit, duration of disease and radiological changes. Fluorosis should be considered as a possible cause of compressive myelopathy secondary to ossification of PLL or LF in the endemic areas and the neurological deficit parallels with duration of disease and radiological changes. Target sign pathognomic of ankylosing spondylitis was seen in two patients.

Keywords : Magnetic resonance imaging, Fluoride poisoning, Ligaments. Spine, cord compression.

INTRODUCTION

Endemic skeletal fluorosis is a chronic metabolic disease caused by ingestion of large amount of fluoride through either water or food in geographic areas where high levels of fluoride occurs naturally. Although the prevalence of this disease has decreased considerably it still occurs in some parts of the world.¹ In contrast to global scenario prevalence of fluorosis is still high in developing countries like India; especially states like Punjab, Haryana, Rajasthan, Andhra Pradesh² are considered endemic for the disease. In Rajasthan, almost 27 districts are considered endemic zones for this disease.

Chronic toxicity of fluoride in human beings manifests predominantly on dental and skeletal tissue. Beside this other organs like thyroid, kidney cardiovascular and hemopoietic systems are also involved. Neurological complications, mainly compressive myelo radiculopathy, occurs in about 10% of skeletal fluorosis.³ Skeletal fluorosis was first reported as an endemic disease in India in 1937⁴. Since then various studies using plain skiagrams⁵, myelography^{6,7}, CT scan⁸ have been used to evaluate, the radiological changes in fluorotic spine but little has been written about spectrum of MRI findings⁹. Since fluorosis affects almost entire spine at multiple levels thus MRI because of its multiplanar capacity is considered superior as it can evaluate entire spine in single study. We evaluated the spectrum of MRI appearance in 18 patients of this disorder with the idea of highlighting its frequent occurrence as a cause of cord compression in endemic areas and to differentiated from other metabolic bone diseases.

MATERIAL & METHODS

This study was carried out in 18 patients of skeletal fluorosis admitted in dept of Neurology BMRC Jaipur India between

Jan 2002 - March 2004. Clinical manifestations included pain and stiffness in the spine, motor and sensory deficits in limbs, radicular pain and retention of urine.

Diagnosis of fluorosis was confirmed on the basis of urinary fluoride levels and AP skiagrams of forearm bones revealing ossification of interosseous membrane (*Fig.1*). Patients were subjected to routine investigations like blood sugar. KFT, LFT urine complete and microscopic, X-Ray fore-arm bones. Apart from these all patients were subjected to MRI of whole spine on 1.5 Tesla super-conducting magnet. T1 and T2 images were obtained using spin echo sequences in axial and saggital planes with slice thickness of 3 mm, interslice gap of 0.4 mm and matrix 195 x 256. Conditions mimicking fluorosis such as : Ankylosing spondylitis, Diffuse idiopathic hyperostosis, Schonberg disease, Secondaries spine were excluded.



Fig.1: X-ray fore arm bones (AP view) showing ossification of interosseous membrane

RESULTS

There was male preponderance (M:F ration=14:4). Most of the patients were active manual workers doing unskilled labour on farms and living in the endemic area since birth. Most of the areas from where they belonged were fairly hot and dry, the temperatures touching 47°C. This necessitates drinking of large quantities of water and thus predisposing to higher amounts of fluoride deposition. The age ranged between 30-75 years (mean age 54 years).

Correspondence: Dr. Ravindra Singh, Department of Neurology, SMS Medical College, Jaipur, Rajasthan, India
e-mail: arihant_12rediffmail.com

Neurological examination revealed mild tenderness and stiffness in spine in 16 patients, quadriparesis in 8 patients, paraparesis in 6 patients, radiculopathy in 12 patients and bladder involvement in 2 patients .

All 18 patients had evidence of cord compression of MRI . Thickening of PLL was identified in 14 patients (77%) out of which 7 patients showed ossification. This thickening was most commonly seen in the cervical region (8 patients) followed by thoracic and cervicothoracic regions. Mean thickness of PLL

Table 1: Posterior longitudinal ligament changes

	No. of patients	Range	Mean duration of illness
Thickening	14	5-9mm	3.6 years
Ossification	7		5.8 years
Site			
Cervical	8		
Thoracic	4		
Cervicothoracic	2		

was 6.7 mm (range 5-9 mm)(table 1).

Ligamentum flavum thickening was seen in 16(88.8%) patients out of which 11 patients (69.2%) had ossified ligamentum flavum (OLF). Ligamentum flavum thickening was most commonly seen in cervicothoracic (9 patients) followed by thoracic (5 patients) and cervical spine (2 patients), the thickness of ligamentum flavum ranged from 6-9 mm with

Table 2: Ligamentum flavum changes

	No. of patients	Mean duration of illness
Thickening	16	3.5 years
Ossification	11	5.4 years
Site		
Cervical	2	
Thoracic	5	
Cervicothoracic	9	



Fig. 2: Sagittal T2 w scans of dorsal spine showing ossified posterior longitudinal ligament and ligamentum flavum thickening causing compressive myeloradiculopathy at multiple levels

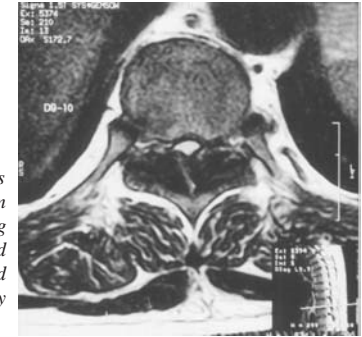


Fig. 3 Axial T2 W scans showing marked ligamentum flavum hypertrophy causing severe canal stenosis and compressing and displacing cord with focal intramedullary hyperintensity.

mean thickness of 7.4mm (table 2). (Fig. 2&3)

Intramedullary hyperintense signals representing cord edema were seen in 17 patients (94%). Neural compression was seen in 9 patients out of which herniated disc and posterior osteophytes were the cause in 6 patients and thickened PLL in 3 patients. Two patients in our series showed alternate bands of low and high signal intensity in intervertebral disc giving target sign appearance(Fig. 4).



Fig. 4 Sagittal T2 W scans of lumbo-sacral spine showing alternating bands of high and low signal intensity (Target sign appearance)

DISCUSSION

Consumption of fluorine contaminated water gives rise to fluorosis as has been reported from many parts of India by Shrott et al⁴, Satyanaryan Murthi et al⁷, SS Jolly et al³. Earliest radiological investigation was plain X-ray. In the later series myelography and CT Scan were used in addition to X-ray. Plain skiagrams show generalized increased bone density with ossification of interosseous membrane and ligaments. Myelography primarily assesses the site of extradural block. Calcification and ossification of spinal ligaments is better seen on CT scan. However MRI is by far the only modality which can give us the complete details of radiological changes in fluorotic spine including ligament calcification ossification, disc protrusion, disc changes, cord and neural foraminal compression and moreover we can visualize the whole spine in a single study.

Ligamentum flavum extends from second cervical to first sacral vertebra and gives low signal on all SE images. Ligamentum flavum thickening more than 3 mm in cervical and thoracic regions and more than 4 mm in lumbar region was considered significant in our study.

Posterior longitudinal ligament is normally seen as thin low intensity linear structure in mid sagittal plane. In parasagittal

plane it is interrupted and is present only at intervertebral levels. Posterior longitudinal ligament thickening of more than 2 mm was considered significant in our study.

Ossified spinal ligaments give signal similar to yellow marrow on T1 and T2 scans¹⁰. Thickening of posterior longitudinal and ligamentum flavum were first reported in 1836 and 1920 respectively and are seen in conditions like ankylosing spondylitis, secondary to trauma, diffuse idiopathic skeletal hyperostosis (DISH), calcium pyrophosphate deposition disease, hematochromatosis and hyperthyroidism¹¹ but still exact cause remains undetermined in many cases.

We found correlation between duration of illness & ossification of PLL and LF. In 7 cases where ossification of PLL was seen the mean duration of disease was 5.8 yrs as compared to 3.6 yrs. where PLL was only thickened & not ossified. Similarly mean duration of disease was 5.4 yrs in 11 cases of if ossification as against 3.5 yrs where LF was only thickened & not ossified. Thus, it takes on an average 5.5 yrs for PLL & LF to become ossified. It was seen that the neurological deficit was more in the patients having ossified ligaments.

Cord edema was seen in 92% cases and a good correlation was observed between extent of extradural compression on MRI and clinical severity. Nine patients had nerve root compression, in six of these it was due to herniated disc and in three patients extensive posterior longitudinal ligament extended far across midline to involve neural foramina. In two cases we noticed an interesting finding of alternating bands of low and high signals in intervertebral disc on T1 and T2W images giving target appearance. They represent dark nucleus pulposus in centre followed by bright inner annulus the dark outer annulus with bright signal of

syndesmophyte marrow at periphery. This appearance is considered characteristic of ankylosing spondylitis. However, this is a preliminary observation which requires further studies to confirm.

Till date only a small series of four cases has been reported by Gupta et al⁸ Our study has shown a direct correlation between duration of disease with neurological deficit and MRI changes, along with this we also observed target sign in 2 patients. These observations were not documented in the earlier study.

Aim of our study was to study the spectrum of MRI changes in fluoritic spine and their correlation with duration of disease and neurological deficit. However, further studies having large sample size are required for correlation of radiological changes on MRI with the prognostic outcome both by conservative and surgical methods.

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DRUG PROFILE

RANOLAZINE

Ranolazine is a compound that is approved by the US FDA for the treatment of chronic angina pectoris in combination with amlodipine, beta-adrenoceptor antagonists or nitrates, in patients who have not achieved an adequate response with other anti-anginals.

Mechanism of Action: The anti-anginal effect of ranolazine does not depend on changes in heart rate or blood pressure. The mechanism of action of ranolazine for anti-anginal effect has not been fully characterised. Ranolazine is an inhibitor of several ion channels, including the late inwards sodium (I_{Na}) current which reduces calcium overload during ischaemic conditions. Reducing excess intracellular calcium can lead to improvement of left ventricular diastolic dysfunction by decreasing diastolic tension and thereby oxygen consumption. Ranolazine has been shown to improve left ventricular regional diastolic function in patients with ischaemic heart disease. Thus, inhibition of the late I_{Na} current by ranolazine is likely to contribute to the anti-anginal effect, but other mechanisms may also be involved.

Pharmacokinetics: Following administration of an oral solution or IR capsule, peak plasma concentrations (C_{max}) are observed within 1 hour. After administration of radiolabelled ranolazine, 73% of the dose was excreted in urine, and unchanged ranolazine accounted for <5% of radioactivity in both urine and faeces. The absolute bioavailability ranges from 35% to 50%. Food has no effect on rate or extent of absorption from the ER formulation. Ranolazine protein binding is about 61-64% over the therapeutic concentration range. Volume of distribution at steady state ranges from 85 to 180 L. Ranolazine is extensively metabolised by cytochrome P450 (CYP)

3A enzymes and, to a lesser extent, by CYP2D6, with approximately 5% excreted renally unchanged. Elimination half-life of ranolazine is 1.4-1.9 hours but is apparently prolonged, on average, to 7 hours for the ER formulation as a result of extended absorption (flip-flop kinetics). Elimination occurs through parallel linear and saturable elimination pathways, where the saturable pathway is related to CYP2D6, which is partly inhibited by ranolazine. Oral plasma clearance diminishes with dose from, on average, 45 L/h at 500 mg twice daily to 33 L/h at 1000 mg twice daily. The departure from dose proportionality for this dose range is modest, with increases in steady-state C_{max} and area under plasma concentration-time curve (AUC) from 0 to 12 hours of 2.5- and 2.7-fold, respectively. Ranolazine pharmacokinetics are unaffected by sex, congestive heart failure and diabetes mellitus. AUC increases up to 2-fold with advancing degree of renal impairment.

Dosages: Initial studies used an oral solution or an immediate-release (IR) capsule, but subsequently an extended-release (ER) formulation was developed to allow for twice-daily administration with maintained efficacy. Usual dose of extended release (ER) is 200mg twice daily.

Drug Interaction: Ranolazine is a weak inhibitor of CYP3A, and increases AUC and C_{max} for *simvastatin*, its metabolites and HMG-CoA reductase inhibitor activity <2-fold. *Digoxin* AUC is increased 40-60% by ranolazine through P-glycoprotein inhibition. Ranolazine AUC is increased by CYP3A inhibitors ranging from 1.5-fold for *diltiazem* 180 mg once daily to 3.9-fold for ketoconazole 200 mg twice daily. *Verapamil* increases ranolazine exposure approximately 2-fold. CYP2D6 inhibition has a negligible effect on ranolazine exposure.