

Fibrous dysplasia & McCune-Albright syndrome: An experience from a tertiary care centre in north India

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Background & objectives: Fibrous dysplasia (FD) is a rare metabolic bone disease and information available from India is limited to only anecdotal case reports. We describe the clinical profile and therapeutic outcome of 25 patients with FD observed over a period of 14 yr in a tertiary care centre from north India.

Methods: In this retrospective study patients (n = 25) with diagnosis of fibrous dysplasia based on either classical radiological features and/or histological evidence on bone biopsy, were analyzed. Associated endocrinopathies if any, were evaluated. The diagnosis of McCune Albright syndrome (MAS) was considered when fibrous dysplasia was accompanied by either café-au-lait macules and/or endocrinopathies. The clinical presentation, biochemical parameters and imaging were analysed. Seven patients received bisphosphonate therapy. The final outcome and side effects were noted.

Results: Age of the patients ranged from 7 to 48 yr (mean \pm SD, 24.2 \pm 11.4 yr) with a lag time between onset of symptoms and presentation ranging from 1 to 20 yr (mean \pm SD, 6.6 \pm 6.2 yr). The mean duration of follow up was 3.5 \pm 2.1 yr. Eighteen (72%) patients had polyostotic disease while the remaining had monostotic FD. Eight patients had endocrinopathies: five had acromegaly, one each had gonadotropin independent precocious puberty (GIPP), hyperthyroidism and hypophosphatemic rickets. One child with GIPP later developed hyperthyroidism. McCune Albright syndrome was observed in 10 (40%) patients. A majority of the patients underwent various minor or major surgical procedures and seven patients received bisphosphonates for recurrent pathological fractures. Bone pain was reduced in all bisphosphonate treated patients with a decrease in subsequent fractures.

Interpretation & conclusions: This series of FD patients from north India shows the varying presentations of this rare disease. Medical treatment with bisphosphonates appears to be potentially rewarding.

Key words Bisphosphonates - endocrinopathies - fibrous dysplasia - McCune-Albright syndrome

Fibrous dysplasia (FD) is a congenital but non-inheritable benign disorder in which medullary bone is replaced by fibro-osseous tissue which causes

distortion and overgrowth of the affected bone¹. FD usually presents with bone pains, deformities, recurrent pathological fractures of the affected site and

sometimes associated with endocrine hyperfunction². There is no gender predilection for FD but it is more common in children and adolescents as compared to adults and older patients³.

Clinically FD is divided into three groups³ (1) monostotic: single bone involvement, which is most common (70%) (2) polyostotic: multiple bone involvement, a less common form (30%), and (3) McCune-Albright syndrome (MAS), a rare variant of mono/polyostotic disease in which FD is associated with café-au-lait macules and/or endocrinopathies^{4,5}. Till recently, treatment of FD has been confined to orthopaedic surgeon for external fixation, bone grafting and curettage⁶⁻⁸. In the last two decades, bisphosphonates have been used extensively for management of various metabolic bone disorders including FD^{9,10}.

Several studies are available on FD from western countries, but from developing countries, information is only available as short report or anecdotal case reports. We report clinical profile and treatment outcome of 25 patients with fibrous dysplasia from a tertiary care centre of north India.

Material & Methods

In this retrospective study medical records of 25 patients of documented fibrous dysplasia (January 1995 to October 2009) were retrieved from the Central Medical Records of Nehru Hospital at the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh. The study protocol was approved by the Institute's Ethics Committee and informed consent was obtained from all the patients who received bisphosphonates. These records were reviewed in a structured proforma for age, sex, symptoms, signs, relevant biochemistry, hormonal profile, treatment modality and outcome. The diagnosis of fibrous dysplasia was based on one or more of the following criteria: classical radiological features of fibrous dysplasia and/or histological evidence of fibrous dysplasia on bone biopsy. McCune Albright syndrome (MAS) was diagnosed if patients with mono/polystotic FD had either café-au-lait macules and/or endocrinopathy.

Fasting blood samples were collected on three consecutive days for estimation of serum calcium, inorganic phosphate, total serum alkaline phosphatase and albumin. Calcium was adjusted for albumin. Relevant skeletal survey was done. In addition, ^{99m}Tc methylene diaphosphonate (MDP) bone scan was performed to assess the extent of disease. Patients

who had symptoms and signs of acromegaly were subjected to growth hormone (GH) suppression test with 75 glucose and MRI head was done to localize the source of GH excess. Other endocrinopathies were investigated including thyroid function test for those who had hyperthyroidism, leutenizing hormone (LH), follicle stimulating hormone (FSH), and estradiol for those who had precocious puberty and appropriate work-up for hypophosphatemia in patients who presented with hypophosphatemic rickets.

Patients with history of fracture in last one year from the time of presentation were offered bisphosphonate therapy. Overall, seven patients received bisphosphonates. Four patients received pamidronate according to protocol (<2 yr of age, 0.5 mg/kg/day for three days; 2 to 3 yr, 0.75 mg/kg/day for three days and greater than 3 yr, 1 mg/kg/day for three days every three monthly for a year). Because of subsequent unavailability of pamidronate, three patients received other bisphosphonates (1 patient received intravenous zoledronate, once yearly, 1 patient received oral alendronate daily and another patient received combined intravenous and intralesional zoledronate which is still experimental)¹¹. Side effects if any, were noted. Bisphosphonates were continued till there was a fracture free period of 1 year. Patients with endocrinopathies were treated accordingly.

Statistical analysis: The statistical program for the social sciences (10.0 PC windows; SPSS Inc. Chicago, IL) was used for data analysis.

Results

Age of the patients ranged from 7 to 48 yr (mean \pm SD, 24.2 \pm 11.4 yr) with a median age of 22 yr. Majority (68%) of the patients had childhood onset of disease. There were 13 males and 12 females with no gender predilection. The lag time from first reported symptom to diagnosis of FD ranged from 1 to 20 yr (mean \pm SD, 6.6 \pm 6.2 yr) and the mean duration of follow up was 3.5 \pm 2.1 yr.

Bone pains (64%), bony deformities (56%), fracture(s) (52%) and facial asymmetry (16%) (Fig. 1) were the common presenting manifestations. There was no significant difference in the frequency of clinical manifestations between males and females. The clinical characteristics of these 25 patients are summarized in the Table.

The diagnosis of FD was based on classical radiological features and/or histological evidence on

Table. Summary of patients with fibrous dysplasia (n=25)

Sr no	Age (yr) at presentation	Sex	Bone involvement (poly/mono)	Endocrinopathy	Café-au-lait macules
1	11	F	P	-	+
2	24	F	P	-	-
3	30	F	P	Hyperthyroidism	-
4	28	M	P	Acromegaly	-
5	25	M	P	Acromegaly	-
6	40	M	P	Acromegaly	-
7	19	F	P	Hypophosphatemic rickets	+
8	17	F	P	-	-
9	22	F	M	-	-
10	11	M	M	-	+
11	15	M	M	-	-
12	22	F	P	-	-
13	10	M	P	-	-
14	19	F	P	-	-
15	14	F	M	-	-
16	19	F	P	-	-
17	48	M	P	Acromegaly	+
18	38	M	M	Acromegaly	-
19	30	M	M	-	-
20	32	M	M	-	-
21	23	M	P	-	-
22	44	F	P	-	-
23	15	M	P	-	-
24	42	M	P	-	-
25	7	F	P	Precocious puberty, hyperthyroidism	+

M, male; F, female; P, polystotic; M, monostotic



Fig. 1. Craniofacial fibrous dysplasia showing asymmetry of face.

bone biopsy. X-ray of the involved bone in all the patients showed typical expansile lytic lesions and some lesions with trabeculated area of radiolucency with or without ground glass appearance (Fig. 2). However, dysplastic lesions in the facial bone were radiodense. Based on these radiological findings, 18 patients (72%) had polyostotic and the remaining seven (28%) had monostotic lesions. Among polyostotic FD, the most commonly involved bones were craniofacial followed by long bones, ribs and orbit. Paranasal sinuses were involved in 11 (44%) patients and maxillary sinus was the most commonly involved. Among monostotic FD, the most commonly involved bone was femur followed by tibia and humerus. Classical Shepherd's Crook deformity was seen in three patients. Thirteen (52%) patients had one or more fractures.

^{99m}TcMDP bone scan was available in 20 patients and 13 of them had polyostotic disease which corresponded with the radiology. Bone biopsy was

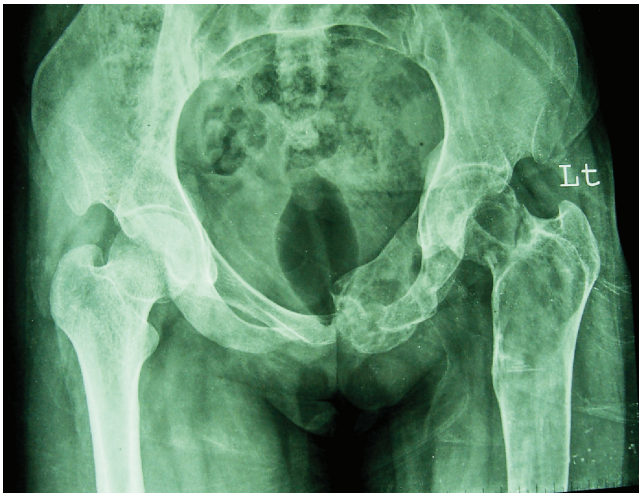


Fig. 2. X-ray pelvis AP view showing multiple expansile lytic lesion with fish net appearance involving left ischium, pubis, left neck of femur and greater trochanter.

available in 18 patients and showed irregular trabeculae of woven bones (chinese letter pattern) without osteoblastic rimming and surrounded by fibrous connective tissue, features characteristic of FD (Fig. 3) and in the remaining patients diagnosis was based on characteristic radiology.

Of the 25 patients, eight (33%) had endocrinopathies. Five patients had acromegaly, one each had gonadotropin independent precocious puberty (GIPP), hyperthyroidism and hypophosphatemic rickets. The child with GIPP later also developed hyperthyroidism. Of the five patients with growth hormone excess, one patient had gigantism while the others had acromegaly. All of them had facial asymmetry and hyperprolactinaemia and four of them had documented pituitary tumour on imaging. One patient with hyperthyroidism had nodular goiter and another had diffuse goiter. Five patients with FD had café-au-lait macules (Fig. 4). MAS was observed in 10 (40%) patients.

Twenty three of the 25 patients underwent minor/major reconstructive surgery for fibrous dysplasia. For endocrinopathies, 4 out of 5 patients with acromegaly underwent pituitary surgery (2 transfrontal and 2 transsphenoidal) and one with toxic adenoma underwent total thyroidectomy and the other was planned for radioablation. Other endocrinopathies were treated accordingly.

Seven patients received bisphosphonates for pathological fractures. Bone pain was reduced in all

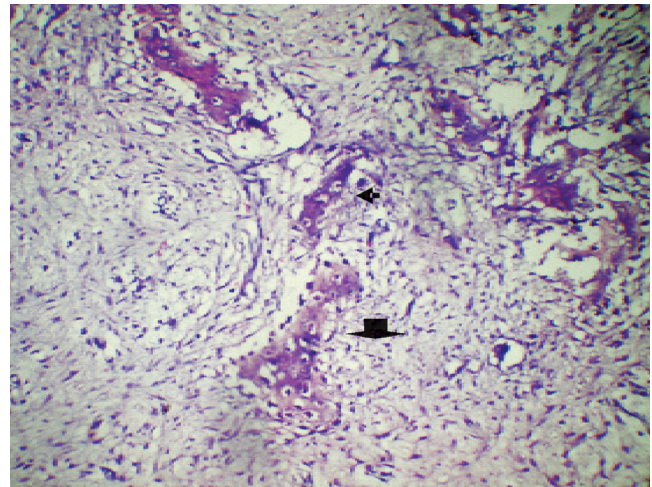


Fig. 3. Histopathology of bone biopsy specimen showing irregular trabeculae of woven bones (chinese letter pattern; small arrow) without osteoblastic rimming (big arrow), surrounded by fibrous connective tissue, features characteristic of FD (H&E, 20X).

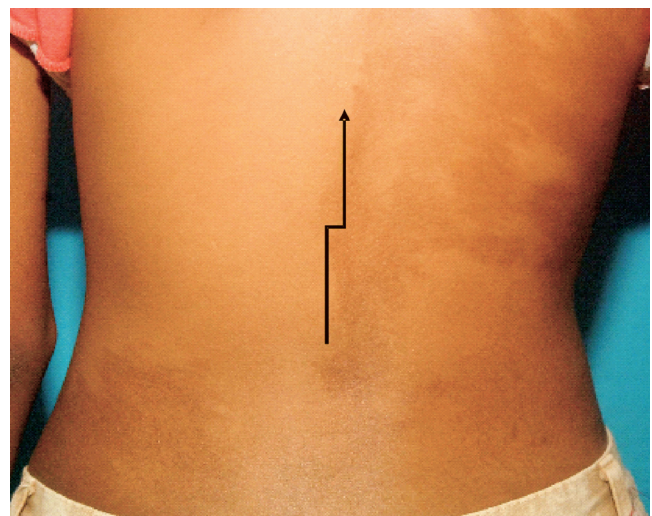


Fig. 4. A large café-au-lait macule (arrow) measuring 10×7 cm over the back with irregular margin and not extending beyond the midline.

bisphosphonate treated patients but none of the patients showed improvement in bone deformity. However, on X-ray the bone lesions showed signs of healing. Five out of seven (72%) patients did not develop any new fracture after bisphosphonate therapy. Three patients who received injectable bisphosphonates developed fever on day 2 of infusion and one patient developed hypocalcemia.

Discussion

This study describes the varying presentations of fibrous dysplasia with various endocrinopathies and

successful use of bisphosphonates in a subset of these patients.

Patients with FD usually present in childhood or early adolescence³ as was seen in our study, in that more than two third of patients had onset of disease before 20 yr of age. The usual lag time between onset of symptoms and clinical presentation varied from months to years in various studies similar to our observation³. Majority of our patients remained undiagnosed for a long period of time and presented later with fractures and endocrinopathies. The most common presenting manifestations are bone pains, deformity and fractures¹² and sometimes isolated endocrinopathies like GIPP³, thyrotoxicosis and acrogigantism. Usually patients with monostotic FD have delayed presentation unless accompanied with endocrinopathies as compared to polyostotic variants. This was not observed in our study as many patients even with endocrinopathies presented at a later age. The male to female ratio was almost same in our study, these findings are similar to others¹².

One of the common presenting manifestation of FD is skeletal fracture(s) and 52 per cent of our patients had one or more fractures, compared to 65 per cent in another study¹². Bone deformity and facial asymmetry were more common in our patients compared to others¹². The high incidence of bone deformities was probably due to delayed presentation. Most commonly involved bones in our study were craniofacial followed by femur, tibia, humerus and ribs as reported by others^{3,13}. Commonly involved paranasal sinus in our study was maxillary sinus followed by sphenoid sinus, however, in one study sphenoid sinus (83%) was more commonly involved compared to maxillary sinus (11%)¹⁴.

Of the 25 patients, eight had endocrinopathy. Most common endocrine abnormality documented in our series was hypersomatotropism (20%)⁵ and hyperprolactinemia (20%) followed by hyperthyroidism¹⁵ (8%), hypophosphatemia¹⁶ (4%) and precocious puberty (4%). However, in a study done in paediatric age group, asymptomatic hypophosphatemia was the most common endocrine abnormality (38.5%) followed by sexual precocity (16.5%)¹⁷. The acromegaly associated with fibrous dysplasia differs from classical acromegaly by its presentation at a younger age, facial asymmetry, hyperprolactinaemia and lack of demonstrable adenoma on imaging in majority of patients⁵. However, in our study 4 out of 5 patients with acromegaly had pituitary adenoma and all had hyperprolactinaemia. Hyperthyroidism

associated with FD is due to autonomous thyroid nodule with constitutive activation of G α subunit of TSH receptor¹⁸. Ablative therapy is the treatment of choice as was done in our patients. Patient who had GIPP later developed hyperthyroidism emphasizing the fact that these patients need continuous surveillance for evolving endocrinopathies. Patients with FD sometimes may present with manifestations of rickets and osteomalacia during childhood and adolescence. Hypophosphatemia is the characteristic abnormality in these patients and is attributed to increased secretion of fibroblast growth factor 23 (FGF23), a phosphatonin secreted from dysplastic bone lesions, hence leading to phosphaturia¹⁶. Only one of our patients had low serum phosphate and florid features of hypophosphatemic rickets¹⁶ in contrast to the findings in another study which reported asymptomatic hypophosphatemia (38.5%) as a more common entity in FD¹².

The diagnosis of FD is based on classical radiological findings substantiated by bone scans and characteristic pathological findings on histopathology. However, sometimes bone lesions particularly in craniofacial regions are not accessible to biopsy. Therefore, the diagnosis rests on classical radiological findings. In our study, histopathology data were available in more than two third of patients.

The pathogenesis of FD involves somatic activating mutation of the gene encoding the alpha subunit of the stimulatory G protein in the bone marrow cells, resulting in locally increased stimulatory activity of adenylyl cyclase and cAMP. This mutation leads to increased production of C-fos protein and interleukin-6 (IL-6) that result in classic dysplastic bone of FD³. The associated endocrinopathies are the result of constitutive activation of G protein coupled receptor by hormones acting through it including LH, FSH, thyroid stimulating hormone (TSH) and growth hormone relating hormone (GHRH) thereby manifesting as GIPP, hyperthyroidism and acromegaly respectively^{4,5,15}.

Till recently, the treatment of FD was only restricted to symptomatic orthopaedic management like correction of fractures, internal fixation, curettage and grafting. The use of bisphosphonate (intravenous pamidronate) in FD showed promising results with remarkable improvement in bone pain and healing of bone lesions¹². Similar effects were later shown by oral alendronate and intravenous zoledronate. The possible mechanism of action of bisphosphonates in FD is related to suppressed osteoclastic activation

which occurs in FD due to constitutive activation of G α subunit in the bone tissue. In our study, those who received bisphosphonates showed symptomatic improvement in bone pain and reduction of fracture incidence, although there was no improvement in bony deformities, a finding similar to other studies^{9,12}. Long term (> 5 yr) bisphosphonates therapy is associated with severe suppression of bone turn over (SSBT) and results in atypical fracture of shaft of long bones¹⁹. The proposed mechanisms for fracture in SSBT include impaired healing of microfractures and altered bone quality though bone mineral density progressively rises¹⁹. SSBT is unlikely to be encountered in patients with FD as prolonged use of bisphosphonates is not recommended.

The major limitations of our study were: it being a retrospective analysis, follow up data were not robust, and limited number of patients received bisphosphonates.

In conclusion, fibrous dysplasia has varied presentation including different endocrine manifestations. Therapy with bisphosphonates may reduce the co-morbidities.

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Conflict of interest: Nothing to declare

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