McCune-Albright Syndrome: The Patterns of Scintigraphic Abnormalities

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This study of 22 patients with the McCune-Albright syndrome examined the scintigraphic distribution of fibrous dysplasia. The most frequently affected areas were the base of the skull (82% of patients), mandible (50%), facial bones (45%), femora (59%), and legs (64%). The least frequently affected areas included the hands (none), wrists (none), ankles (none), feet (5%), sacrum (5%), and vertebrae (9%). The distribution varied somewhat from idiopathic fibrous dysplasia but generally agreed with the distributions reported in radiographic studies of patients with the McCune-Albright Syndrome. The serum alkaline phosphatase was not an accurate predictor of the extent of fibrous dysplasia.

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The McCune-Albright syndrome is a rare condition characterized by precocious puberty, polyostotic fibrous dysplasia, and, often, cafe-au-lait skin pigmentation. Varying forms of the syndrome have been documented (*1–6*). Ninety-five percent have been females. Although the pattern of cafe-au-lait spots may implicate a dominant lethal gene defect (*7*), all reported cases have been sporadic with no known hereditary basis. The pathophysiology which underlies the diverse manifestations is not understood although recent endocrine investigations have indicated that the precocious puberty results from autonomous ovarian hyperfunction (*8*).

The polyostotic fibrous dysplasia component of the McCune-Albright syndrome exhibits a wide spectrum of clinical severity. Patients with extensive bone disease may present in early childhood with fractures and deformities of the long bones. When these patients suffer femoral involvement, a bowed appearance, referred to as a "shepherd's crook deformity" (*9*), may result. Patients with moderate bone disease may have impaired ambulation due to limb length discrepancies. Another common site of involvement is the skull. In some cases, surgical correction has been necessary to resolve progressive facial and skull deformities. Mild bone disease without fractures or deformities may not be detected without a radiographic examination. Characteristically, the radiographs exhibit a widened medullary cavity and cortical thinning with a "ground-glass" appearance replacing the normal trabecular architecture. Even radiography may fail to identify active fibrous dysplasia in some mildly affected patients, especially when regions such as the base of the skull are affected. Bone scintigraphy has helped establish the presence and extent of bone involvement in such cases (*10,11*). The superior sensitivity of bone scintigraphy over conventional radiology was anticipated based upon studies of small numbers of patients with polyostotic fibrous dysplasia (*12–14*).

Reports of patients with classical McCune-Albright syndrome have not addressed bone scintigraphy (*6,15*). This study reports the distribution of scintigraphic abnormalities in a group of patients referred for evaluation of precocious puberty who have the classical endocrine and osseous manifestations of the McCune-Albright syndrome and are followed at this facility.

MATERIALS AND METHODS

Twenty-two females, age 2 to 14 yr (mean ± s.d. = 5.9±3 yr), were diagnosed as having the McCune-Albright syndrome based on the presence of precocious puberty and fibrous dysplasia of bone. Cafe-au-lait spots, not required for the diagnosis, were found in 14 patients. Precocious puberty in girls is defined as development of breasts and/or pubic hair before the age of 8 yr together with accelerated linear growth and bone age advancement (*8*). The extent of breast development and pubic hair growth was measured using Tanner staging (*16*). The presence of bone involvement was determined by radiographic and scintigraphic examinations. Clinically, patients were classified as extensively, moderately, or mildly affected. Severely affected patients had more than one fracture per year, impaired ambulation or immobilization and clinically evident skull deformities. Moderately affected patients had limb asymmetry and approximately a once per year fracture frequency. Mildly affected patients had no significant limb asymmetries or deformities and few, if any, fractures.

Bone scintigraphy was performed on each patient using i.v. technetium-99m-methylene diphosphonate (^{99m}Tc-MDP) at a

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dose proportional by weight to a 925-MBq (25 mCi) adult dose. Approximately 3 hr after injection, images were obtained in multiple projections. Each study was read by an experienced observer who tabulated any abnormalities by skeletal region. Later, contemporaneous radiographic examinations, when available, were compared to the scintigraphic findings.

Serum alkaline phosphatase has been shown to generally correlate with skeletal involvement in fibrous dysplasia (*17*). Our study compared the serum alkaline phosphatase obtained within days of the bone scintigraphy to extend that relationship by determining whether the serum alkaline phosphatase also corresponded with the extent to which the fibrous dysplasia was distributed though the skeleton.

RESULTS

Table 1 lists each subject along with her clinical severity, age, Tanner stage, clinical evidence of cafe-au-lait pigmentation, and serum alkaline phosphatase. Table 2 depicts the scintigraphically identified skeletal abnormalities by region and frequency. The skull was involved in all but three cases (86%)—most frequently in the base (18 patients, 82%). Other frequent sites of skeletal involvement were the femora (59%), legs (64%), mandible (50%), and facial bones (45%). The areas least commonly affected were the hands (none), wrists (none), ankles (none), feet (5%), sacrum (5%), and vertebrae (9%). The average percentage of bone involvement was 31±23% (mean ± s.d.). One patient (5%) had one area of involvement (monostotic fibrous dysplasia). Scintigraphic and radiographic evidence of fibrous dysplasia varied slightly. Of 140 scintigraphically identified sites, 42 (30%) were radiographed with 27 (64%) showing abnormalities consistent with fibrous dysplasia and 15 (36%) considered normal. Interestingly, the modalities also differed when a site was judged scintigraphically normal. Of these 344 sites, 111 (32%) were radiographed with 104 (94%) also considered normal while 7 (6%) were considered consistent with fibrous dysplasia.

TABLE 1
Characteristics of the Subjects

Patient no.	Clinical severity	Age (yr)	Tanner stage		Cafe-au-lait pigmentation	Serum Alk phos
			Breast	Pubic hair		
1	+++	14	V	V	yes	795
2	+++	6	IV	IV	yes	470
3	+++	5	III	II	yes	890
4	+++	4	III	II	yes	209
5	+++	4	II	IV	yes	2550
6	++	8	II	I	no	1155
7	+	4	II	I	yes	285
8	+++	2	IV	I	yes	1935
9	+	8	III	I	yes	602
10	+	10	IV	II	no	332
11	++	5	III	I	yes	343
12	++	4	II	I	yes	374
13	+	9	IV	III	no	133
14	++	5	II	I	no	286
15	+	10	IV	I	no	243
16	+	5	II	II	no	267
17	+	5	III	II	yes	571
18	+	7	IV	II	no	228
19	+	8	II	II	yes	204
20	++	4	IV	III	yes	311
21	++	1	II	I	yes	345
22	+	2	II	I	no	154
Totals					14 (64)%	

+++ = severe clinical disease.
++ = moderate clinical disease.
+ = mild clinical disease.
Serum Alk Phos = serum alkaline phosphatase (U/l) [for females aged 6–17, the normal mean ± s.d. = 362 ± 78].

The serum alkaline phosphatase levels for the 22 McCune-Albright patients are shown in Table 1 and are compared to the range of serum alkaline phosphatase in a group of 27 normal girls age 6–17 yr (mean ± s.d. = 11.5±6 yr). Eight out of the 22 (36%) McCune-Albright patients had elevated alkaline phosphatase levels. These patients did not differ from the remainder of the group by age, clinical severity, or number of abnormal scintigraphic sites.

The incongruity between serum alkaline phosphatase and scintigraphic evidence of fibrous dysplasia in these patients is illustrated by two patients. Patient 2 was a 6-yr-old with a history of cafe-au-lait pigmentation, vaginal bleeding at 3 mo of age, and early breast development. An abnormal radiographic survey, abnormal ^{99m}Tc-MDP scintigram with 65% of the skeletal regions abnormal (Fig. 1), and slightly elevated alkaline phosphatase (470 U/l) were consistent with polyostotic fibrous dysplasia.

Patient 8 was a 2-yr-old girl with cafe-au-lait pigmentation noted at birth, breast development at 6 mo of age, regular menses at 16 mo, and both radiographic and scintigraphic evidence of polyostotic fibrous dysplasia. Progressive left maxillary growth due to her fibrous dysplasia required surgical correction at age 4 yr. She had a high alkaline phosphatase level (1935 U/l). However only 35% of her skeleton was scintigraphically involved.

DISCUSSION

The increased vascularity of lesions in fibrous dysplastic lesions as demonstrated by early perfusion bone imaging has been postulated as the cause of the abnormally high intensity of those lesions (*10*). Although not as sensitive as scintigraphy (*10*), conventional radiologic examinations characteristically identify fibrous dysplasia as demonstrating sclerosis, deformation, expansion with cortical thinning, and as showing an overall ground glass appearance (*9,12,13,16*). Radiographs of two McCune-Albright patients show these characteristics, including severe shepherd's-crook deformities of

TABLE 2
Distribution of Abnormalities by Patient and Location

Bones/ Regions	Patient Number																					Total (%)
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	
Base of skull	+	+	±	+	◇	+	±	±	±	±	+	±	+	±	±	+	◇	+	±	◇	±	◇	18(82)
Legs	+	+	+	+	+	+	◇	±	±	±	+	◇	◇	±	◇	◇	+	◇	◇	+	◇	±	14(64)
Femora	+	+	+	+	+	+	◇	±	◇	±	◇	±	+	±	◇	◇	+	◇	◇	+	◇	◇	13(59)
Mandible	+	+	+	+	+	+	+	±	◇	◇	◇	◇	+	+	+	◇	◇	◇	◇	◇	◇	◇	11(50)
Facial	+	+	±	◇	+	+	±	±	◇	◇	◇	+	◇	◇	◇	+	◇	+	◇	◇	◇	◇	10(45)
Maxilla	◇	+	+	+	+	◇	+	+	+	◇	◇	◇	+	◇	+	◇	◇	◇	◇	◇	◇	◇	10(45)
Ischium	+	+	+	+	+	+	◇	◇	◇	+	◇	◇	◇	+	◇	◇	◇	◇	◇	◇	◇	◇	8(36)
Humeri	+	+	±	+	+	◇	◇	◇	±	◇	◇	+	+	◇	◇	◇	◇	◇	◇	◇	◇	◇	8(36)
Pubis	+	◇	+	◇	+	◇	◇	◇	◇	+	+	◇	◇	+	◇	◇	+	◇	+	◇	◇	◇	8(36)
Ilium	+	+	+	+	+	+	◇	◇	◇	+	+	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	7(27)
Occipital	+	◇	±	+	◇	+	+	◇	◇	◇	◇	+	◇	◇	◇	◇	◇	◇	◇	◇	+	◇	7(32)
Parietal	+	◇	+	◇	◇	+	±	±	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	+	◇	5(23)
Ribs	+	+	◇	+	◇	+	+	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	5(23)
Frontal	+	+	◇	◇	+	◇	+	◇	◇	◇	+	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	5(23)
Forearms	+	+	◇	+	◇	+	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	4(18)
Scapula	+	+	◇	◇	+	◇	◇	◇	+	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	4(18)
Vertebrae	+	◇	◇	◇	◇	◇	◇	◇	+	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	2 (9)
Sacrum	+	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	1 (5)
Feet	+	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	1 (5)
Hands	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	0
Wrists	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	0
Ankles	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	0
Skull																							19(86)
Extremities																							15(59)
Axial																							12(54)

+ = Abnormal by scintigraphy.
◇ = Normal by scintigraphy.
Underlined when contrary to x-ray findings; double underlined when confirmed by x-ray.

the femora. Although fibrous dysplasia was not confirmed by biopsy, other causes for the increased focal tracer uptake such as cancer, Paget's disease, and fractures are unlikely in view of the patients' ages and symptomatic histories. Moreover, the lesions failed to retain the normal outline of the bones, and thus were not typical of Paget's disease (*10*). While pathologic fractures are present in 85% of patients with idiopathic fibrous dysplasia, the incidence of fractures in McCune-Albright patients is lower, 33% (*15*).

Harris et al. (*9*) documented the frequency of individual bone involvement for 37 patients with polyostotic fibrous dysplasia. That distribution, like the one in our study, showed frequent involvement of the base of the skull (50%), facial bones (40%), femur (92%), tibia (81%), fibula (62%) as well as less frequent involvement in the vertebrae (cervical, 7%; lumbar, 14%). However, Harris et al. found frequent involvement in areas not commonly affected in our population: the ribs (55%), pelvis (78%), carpals (56%), tarsals (73%), metatarsals (61%), and ankles (30%). These discrepancies may be due to differences between idiopathic fibrous dysplasia and fibrous dysplasia associated with the McCune-Albright syndrome. These differences are important when considering whether these regions should be included in routine bone scintigraphy of these patients. Of the 37 patients with fibrous dysplasia in the Harris et al. study, 11 (30%) also had precocious puberty. The distribution seen in this subgroup of patients is very similar to the McCune-Albright group, with one patient having 5% of her skeleton involved, one with 10%, two with 15%, three with 30%, one with 35%, two with 60%, and one greater than 75%.

Since the serum alkaline phosphatase did not significantly correlate with the extent of fibrous dysplasia in these subjects, it may be that these patients have a mismatch between the severity of their osseous involvement and the extent to which the disease is distributed throughout the skeleton. Further studies are needed to examine this possibility.

The largest study conducted on McCune-Albright patients (*6*) contains little data on bone involvement. However, of 10 patients with precocious puberty, four (40%) had fibrous dysplasia at the base of the skull, slightly fewer than in our group. Lee (*15*) studied 13 female McCune-Albright patients, of whom 9 (69%) had fibrous dysplasia confirmed by radiography, including 7 (78%) with sclerosis at the base of the skull.

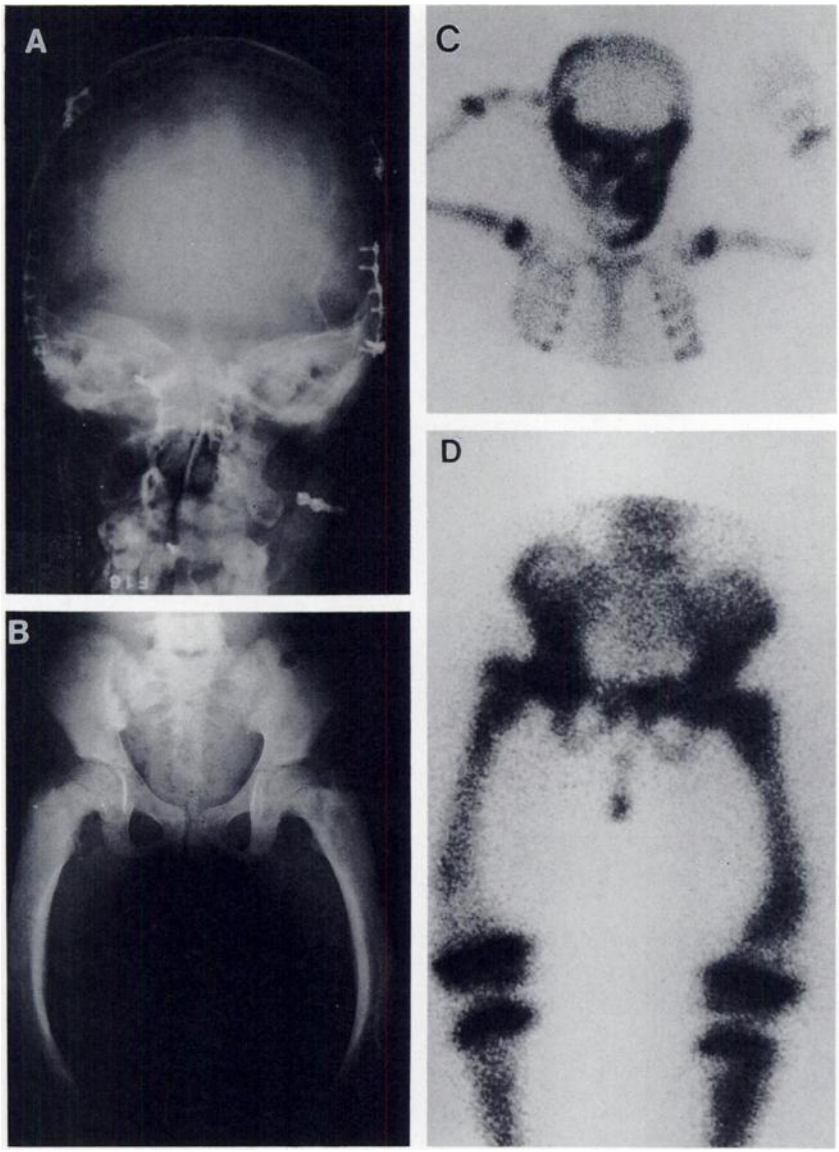

FIGURE 1
Patient 2 had a relatively low serum alkaline phosphatase but widespread fibrous dysplasia as seen on the skull (A) and femoral (B) radiographs and corresponding scintigrams (C) and (D), respectively.

The frequency of scintigraphically identifiable involvement of individual bones in the McCune-Albright syndrome is sparsely reported. This study supports those other works and goes further in defining which areas are involved. Moreover, it shows that serum alkaline phosphatase, a known marker of bone activity, although elevated in 78% of McCune-Albright patients at the time of bone scintigraphy, did not predict the extent of fibrous dysplasia.

The cause and therefore the significance of these skeletal lesions remains unknown. Recently, Kaplan et al. found estrogen and progesterone receptors present in osteogenic cells of a McCune-Albright patient (*18*). With this potentially direct relationship between estrogen and human bone cells, it would be interesting to see if the presence of estrogen receptors corresponds to the frequency of involvement of certain bones in these patients.

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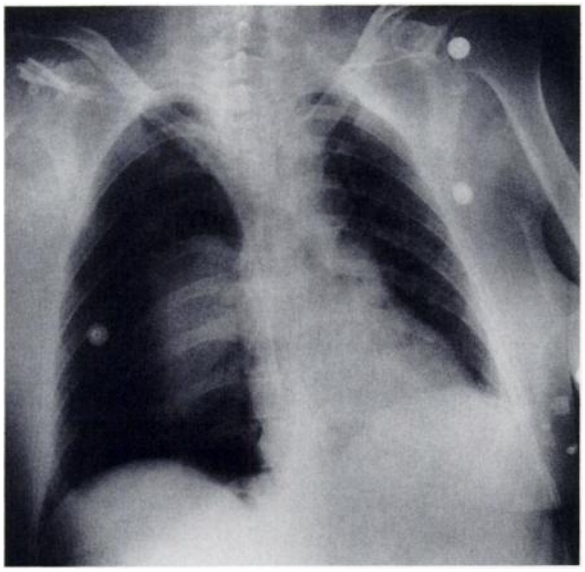
(continued from page 5A)

FIRST IMPRESSIONS



ACQUISITION INFORMATION:
A 57-yr-old female with multiple medical problems was admitted to the MICU with fever of unknown origin and hypotension. A ^{111}In-labeled leukocyte scan was performed to localize a septic source. The WBC scan demonstrates a relative photopenic defect of the lateral right lung field extending from base to apex. Immediately medial to this defect is an area of increased activity. A CXR performed 24 hr prior to this study was unremarkable.

A supine AP CXR, performed immediately after the WBC study demonstrated a right tension pneumothorax. A right subclavian central line had been placed 36 hr prior to study.

TRACER:
Indium-111-labeled autologous WBC

ROUTE OF ADMINISTRATION:
Intravenous injection

TIME AFTER INJECTION:
24 hr

INSTRUMENTATION:
Siemens Body Scan

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