A Novel Syndrome of Mandibular Hypoplasia, Deafness, and Progeroid Features Associated with Lipodystrophy, Undescended Testes, and Male Hypogonadism

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Context: Mandibuloacral dysplasia (MAD) is an autosomal recessive progeroid disorder associated with type A (partial) or B (generalized) lipodystrophy and is due to mutations in lamin A/C (*LMNA*) or zinc metalloproteinase (*ZMPSTE24*) genes.

Objective: The objective of the study was to report a novel syndrome with some overlapping features with MAD.

Results: We report seven patients with mandibular hypoplasia, deafness, progeroid features (MDP), and associated lipodystrophy. These patients have similar features to MAD patients such as hypoplastic mandible, beaked nose, stiff joints, and sclerodermatous skin. However, the patients did not harbor any disease causing variants in *LMNA* or *ZMPSTE24* and showed distinct characteristics such as sensorineural hearing loss and absence of clavicular hypoplasia and acroosteolysis. All males with MDP had undescended testes and were hypogonadal. One adult female showed lack of breast development. Skinfold thickness, dual-energy X-ray absorptiometry and whole-body magnetic resonance imaging for body fat distribution revealed a lack of lipodystrophy in a prepubertal female but a progressive loss of sc fat presenting with partial lipodystrophy in young adults and generalized lipodystrophy in older patients.

Conclusions: Patients with MDP syndrome have a few overlapping but some distinct clinical features as compared with MAD, suggesting that it is a novel syndrome. The molecular basis of MDP syndrome remains to be elucidated. (*J Clin Endocrinol Metab* 95: E192–E197, 2010)

Mandibuloacral dysplasia (MAD; Online Mendelian Inheritance in Man 248370, 608612) is a heterogeneous autosomal recessive disorder characterized by mandibular hypoplasia, dysplastic clavicles, acroosteolysis, prominent eyes, stiff joints, beaked nose, sclerodermatous skin, alopecia, and mottled hyperpigmentation (1–3). We described two distinct patterns of lipodystrophy in patients with MAD: type A with partial loss of sc fat from the extremities and excess fat deposition in the neck and trunk and type B with more generalized loss of sc fat

Abbreviations: MAD, Mandibuloacral dysplasia; MDP, mandibular hypoplasia, deafness, progeroid features.

(1, 2). Type A MAD phenotype was then linked to mutations in the lamin A/C (*LMNA*) gene (4). Genotyping of our initial patients with MAD revealed lack of disease causing *LMNA* mutations in some with type B phenotype (5). Based on a candidate gene approach, we discovered the second MAD locus, zinc metalloproteinase (*ZMPSTE24*) (6). Limited data show that children with MAD due to *ZMPSTE24* mutations may have mild lipodystrophy of the trunk and extremities, whereas adults may have more severe loss of sc fat (6–8).

In our original paper, a 25-yr-old male with MAD type B had no acroosteolysis or clavicular hypoplasia (1) and had no mutations in *LMNA* or *ZMPSTE24* genes (5, 6). We now report six additional patients, all of whom share many phenotypic characteristics, which are distinct from those reported in classical MAD patients with *LMNA* or *ZMPSTE24* mutations.

Patients and Methods

All patients or their parents gave written informed consent. The study protocol was approved by the Institutional Review Boards of the University of Texas Southwestern and the National Institutes of Health. The salient clinical features of the patients are presented in Table 1, Fig. 1, and below. All of them had mandibular hypoplasia, a beaked nose with bird-like facies, prominent eyes, small mouth, growth retardation, limb muscle atrophy, skin atrophy, and hearing loss in childhood but none of them had acroosteolysis or clavicular hypoplasia. All five males had undescended testes and hypogonadism requiring testosterone replacement. All of them were sporadic, isolated cases with no consanguinity among parents (Supplemental Fig. 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org.).

Mandibular hypoplasia, deafness, progeroid features (MDP) patient 100.3

This 63-yr-old male has been published previously (9, 10). Briefly, he noted thinning of extremities and crowded teeth at age 4 yr. His atrophic, undescended testes were surgically removed at age 12 yr. He had a high-pitched voice. He underwent a three-vessel coronary artery bypass graft at age 55 yr, developed diabetic neuropathy, and had an amputation above the left knee at age 58 yr.

MDP patient 200.5

Since the last report as MAD 400.5 (5), this 36-yr-old male developed bilateral corneal opacities in the lower quadrant and had surgery for exposure keratitis. His eyelashes were long. He had a very small uvula and mouth. The skin was taut distally over the feet and multiple telangiectasia were noted on the trunk and thighs. He had limited mobility of the ankle and knee joints. Radiographs of the right foot revealed a hypoplastic fourth metatarsal, a surgically removed fifth metatarsal and eroded distal phalanx of the great toe. The left foot appeared normal.

MDP patient 300.4

This 19-yr-old Italian female had reduced growth and thin limbs since age 4 yr. She had menarche at age 12 yr. At age 16 yr, hepatic steatosis, insulin resistance, impaired glucose tolerance, and hypertriglyceridemia were noted; and rosiglitazone, gemfibrozil, and fish oil were started. Liver biopsy at age 18 yr revealed nonalcoholic steatohepatitis with moderate fibrosis. She underwent bilateral mammoplasty recently for lack of breast development but had regular menstrual periods. She had generalized loss of sc fat and skin on the distal extremities was extremely tight.

MDP patient 400.3

This 10-yr-old Canadian girl started losing fat from the extremities and subsequently from the face, neck, and chest at age 2 yr. She had bilateral coxa valga and could not make a fist. She had long eyelashes and the skin around the eyes was tight. She had a prominent forehead, low-set ears, and prominent upper teeth. She had no breast development. She had some telangiectasia on the ankles. She had notable fat loss from the face, palms, and soles, but her extremities and abdomen were spared. She had mild contractures of the wrists, elbows, ankles, and knees.

MDP patient 500.4

This 25-yr-old Indian male noted thinning of the limbs with associated weakness at age 2 yr. Subsequently he developed scleroderma-like skin changes with ulceration, telangiectasia, and tiny hemangiomas. Hypertriglyceridemia developed at age 16 yr followed by diabetes and osteoporosis. He was on thiazolidinedione and testosterone therapy. Radiographs at age 18 yr revealed congenital fusion of the trapezoid, capitates, triquetral and pisiform carpal bones, scalloping of articular margins of lumbar 1 and 2 vertebrae, and slipped femoral epiphyses bilaterally.

MDP patient 600.4

This 21-yr-old Hispanic male developed generalized loss of sc fat at age 4 yr. He had surgical removal of undescended testes. He had received GH from age 8 to 13 yr and hydrocortisone for adrenal insufficiency. He also had nephrolithiasis and recurrent nose bleeds. He had generalized loss of sc fat and tight skin over the feet and arms. His upper eyelashes were long, and he had bilateral exophthalmos and corneal opacities in the right eye. He had a small uvula. He had contractures of both the ankles and knees. He had plantar calluses and little body hair. Radiographs revealed short fifth metatarsal bilaterally and lack of closure of the distal radial epiphyses (Supplemental Fig. 2).

MDP patient 700.3

This 18-yr-old German male had prominent eyes and a pinched nose. Malformation of the ears was noted at age 6 yr. He underwent bilateral orchiopexy at the age of 3 yr but has been on testosterone replacement since age 15 yr. Generalized lipodystrophy, hypertriglyceridemia, and hepatic steatosis were diagnosed at age 15 yr. He had telangiectasia on the chest and neck and contractures of the fingers, hands, elbows, knees, and ankles.

Methods

Anthropometric measurements, whole-body magnetic resonance imaging (MRI), and dual-energy x-ray absorptiometry for

TABLE 1. Clinical characteristics, body composition, and metabolic variables of the MDP patients

	100.3	200.5	300.4	400.3	500.4	600.4	700.3
Age/sex	63/M	36/M	19/F	10/F	25/M	21/M	18/M
Age at onset (yr)	4	7	4	2	2.5	4	3
Ethnicity	American	American	Italian	Canadian	Indian	Hispanic	German
Birth weight (kg)	3.4	3.2	3.8	3.6	3	4.1	3.9
Height (m)	NA	1.75	1.60	1.19	1.68	1.61	1.79
Weight (kg)	NA	45.4	45	17.2	41.3	55.1	47
BMI (kg/m^2)	NA	14.9	17.6	12.2	14.6	21.3	14.7
Lipodystrophy	+	+	+	−	+	+	+
Joint contractures	+	+	−	+	−	+	+
Telangiectasia	NA	+	−	−	+	−	+
Deafness (age of onset, yr)	+ (18)	+ (15)	+ (7)	+ (8)	+ (16)	+ (14)	+ (6)
Lack of breast development	NA	NA	+	NA	NA	NA	NA
Corneal keratosis	NA	+	−	−	−	+	−
Hepatic steatosis	NA	−	+	−	NA	+	+
Hepatomegaly	NA	−	+	+	NA	−	+
Hypertriglyceridemia (age of onset, yr)	+ (26)	+ (7)	+ (16)	−	+ (16)	+ (21)	+ (15)
Diabetes mellitus (age of onset, yr)	+ (52)	−	−	−	+ (23)	−	−
HDL-C (mg/dl)	NA	27 (>40)	16 (>50)	34 (>50)	NA	25 (>40)	42 (>40)
Leptin (ng/ml)	NA	1.77 (6.0 ± 0.42)	8.22 (12.9 ± 8.9)	4.03	4.36 (4.5 ± 0.48)	7.08 (5.3 ± 0.28)	1.48
Fasting insulin (μU/ml)	NA	8.7 (7.87 ± 0.17)	33.8 (7.87 ± 0.17)	34.1	24.4 (7.87 ± 0.17)	105.4 (9.6 ± 0.24)	17.4
Two-hour PP insulin μU/ml)	NA	400.3	290.6	202.9	NA	558.4	NA
Whole-body fat (% body mass)	NA	15.3 (26.6 ± 6.0)	20.2 (35.1 ± 7.2)	29.9	22.6 (24.6 ± 6.5)	21.1 (24.4 ± 6.1)	14.3
Truncal fat (% regional mass)	NA	19.3	23.7	28.3	30	25.8	19.2
Arm fat (% regional mass)	NA	9.3	20.4	43.9	6.9	21.3	4.8
Leg fat (% regional mass)	NA	5.3	13.9	34.3	7.5	11.8	4.7
Truncal fat (%)/leg fat (%)	NA	3.64 (1.02 ± 0.16)	1.71 (0.76 ± 0.16)	0.83	4.27 (0.93 ± 0.15)	2.19 (0.89 ± 0.13)	4.08

Normal values for some variables are shown in *parentheses* as mean ± SD and for HDL-C as >40 for males and >50 for females. Normal values of leptin are from Ruhl and Everhart (12); insulin from Meng *et al.* (18); and total and percent truncal fat/percent leg fat from Kelly *et al.* (11). Normal values for leptin in children younger than age 20 yr are not available. Normal values for regional body fat (truncal, arm, and leg) are not available. M, Male; F, female; NA, not available; PP, postprandial; HDL-C, high-density lipoprotein cholesterol.
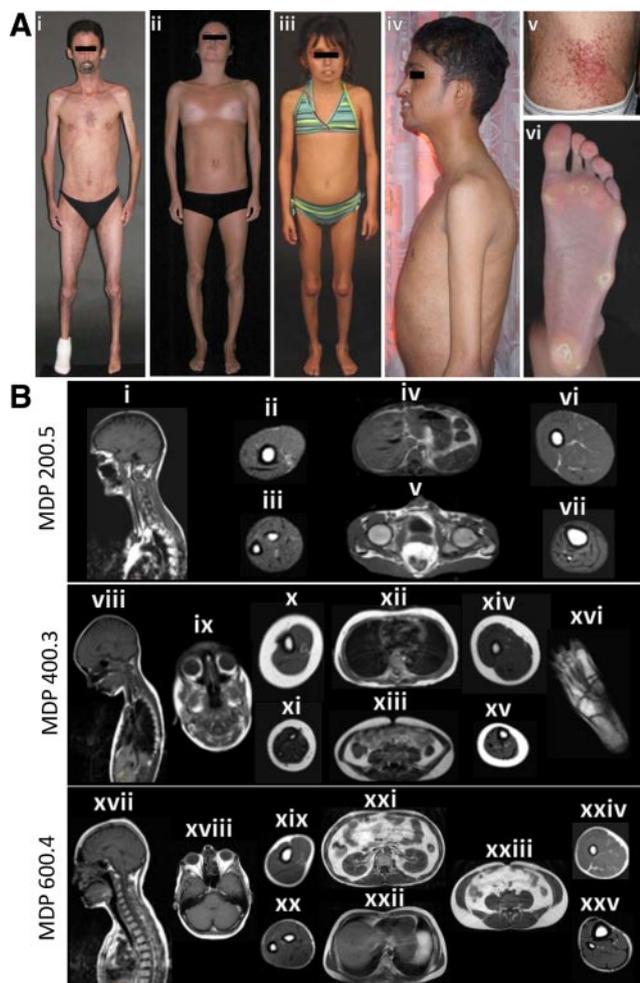
FIG. 1. MDP patients and their body fat distribution pattern on MRI. A, i, MDP 200.5, anterior view of a 36-yr-old male showing generalized lipodystrophy, reduced muscle mass, and prominent maxillary incisors. He had pinched nose, small mouth, and contractures of the elbows. There was no loss of scalp hair and he had graying of hair on the chin. ii, MDP 300.4, anterior view of a 19-yr-old Italian female showing generalized lipodystrophy and lack of breast development. She had pinched nose and small mouth. iii, MDP 400.3, anterior view of a 10-yr-old French Canadian girl with small mouth, pinched nose, and bilateral coxa valga. Her body fat distribution was normal. iv, MDP 500.4, lateral view of a 25-yr-old Indian male showing generalized lipodystrophy, muscle wasting, and prominent maxillary incisors. v, Telangiectasias on the abdomen of MDP 200.5. vi, Marked loss of sc fat from the sole and calluses in the patient MDP 200.5. B, Sagittal T-1-weighted MRIs of the head, neck, and thorax through midline or orbit and axial MRIs of the chest, abdomen, arm, forearm, thigh, calf, and foot from various MDP patients. MRIs of MDP 200.5 show near total loss of sc fat from the head, neck, and thorax (i), arm (ii), forearm (iii), abdomen (iv and v), thigh (vi), and calf (vii). Retroorbital, ip, and bone marrow fat depots were well preserved. MRIs of MDP 400.3 show normal amounts of sc fat in the head and neck (viii and ix), and thorax (xii), normal retroorbital (ix), ip (xiii), retroperitoneal, and bone marrow fat as well as in the arm (x), forearm (xi), thigh (xiv), and calf (xv). Plantar fat (xvi) was reduced. MRIs of MDP 600.4 show moderate loss of sc fat in all the areas including the head and neck (xvii), thorax (xxii), arm (xix), forearm (xx), thigh (xxiv), and calf (xxv). Retroorbital (xviii), intraabdominal, and bone marrow fat depots were well preserved. A significant amount of intraabdominal (xxi and xxiii) fat was noted.

regional and total body fat were performed as described previously (1). Fasting serum insulin and leptin levels were determined by immunoassays using commercial kits (Millipore, Billerica, MA). Fasting serum glucose and lipoproteins were analyzed as part of a systematic multichannel analysis (Synchron CX9 ALX clinical system; Beckman, Fullerton, CA). A standard oral glucose tolerance test for 180 min was performed (1). The exons and exon-intron boundaries of the *LMNA* and *ZMPSTE24* genes were sequenced in genomic DNA obtained from patients' blood according to Simha *et al.* (5) and Agarwal *et al.* (6). Three highly polymorphic short tandem repeats from ABI linkage mapping sets version 2.5 (Applied Biosystems, Foster City, CA) around *LMNA* and *ZMPSTE24* were genotyped in five pedigrees according to the manufacturer's protocol.

Results

Measurement of skinfold thickness revealed severe generalized loss of sc fat in MDP 200.5. MDP 600.4 showed moderate fat loss from the extremities but preserved truncal fat (Supplemental Fig. 3). The prepubertal girl, MDP 400.3, did not have evidence of fat loss.

MDP 200.5, 300.4, 600.4, and 700.3 had moderate to severe reduction in body fat compared with age- and gender-matched normal data (11), whereas MDP 400.3 and 500.4 did not show reduction in body fat (Table 1). The ratio of truncal fat to leg fat, however, was markedly increased in all adult patients (1.7 to 4.1 compared with normal mean values of 0.8 to 1.0; Table 1). Whole-body MRI studies further confirmed the generalized lack of body fat in patients MDP 200.5 and 600.4 with preservation of retroorbital, intraabdominal, and bone marrow fat depots (Fig. 1B). MRIs of MDP 400.3 showed only loss of plantar fat (Fig. 1B). MRI of MDP 700.3 demonstrated a drastic reduction of sc fat.

Serum leptin levels ranged from low to normal (Table 1) (12). Despite a normal glucose tolerance test, MDP 400.3 and MDP 600.4 had markedly elevated fasting and postprandial insulin levels (Table 1). MDP 200.5 and MDP 300.4 had impaired glucose tolerance and hyperinsulinemia (Table 1). MDP 500.4 had diabetes and fasting hyperinsulinemia.

Screening of the exons and the adjacent introns and splice sites revealed no disease causing variants in *LMNA* or *ZMPSTE24* genes in any of the patients. Haplotype analysis of short tandem repeats ruled out linkage to *LMNA* in MDP 200, 300, and 500 pedigrees and to *ZMPSTE24* in MDP 200 pedigree (Supplemental Fig. 1).

Discussion

Our current reports and the review of the literature suggest that these patients represent a novel variety of progeroid

syndrome with lipodystrophy. Freidenberg *et al.* (2) also reported two males (16 and 17 yr old) who had some clinical features similar to MDP patients such as bilateral sensorineural hearing loss, normal clavicles, hypogonadism, and partial lipodystrophy. Unfortunately, no pictures or other details of the patients were published.

None of our patients had any disease causing mutations in *LMNA* or *ZMPSTE24* genes, and linkage to these loci was excluded in some pedigrees. Review of the pedigrees reveals lack of consanguinity or other affected siblings. Thus, MDP syndrome may be due to either autosomal recessive inheritance or *de novo* heterozygous mutations. So far, there is no evidence of transmission because all of the affected males have been hypogonadal. However, females may not be infertile as evidenced by one of our post pubertal patients who had regular menstrual cycles.

MDP patients share only some clinical features with MAD patients reported to harbor *LMNA* or *ZMPSTE24* mutations (13) but reveal many distinct features (Supplemental Table 1). For example, all three varieties have mandibular hypoplasia, short stature, some joint contractures, and sclerodermatous skin with mottled pigmentation. Interestingly, the onset of sc fat loss reportedly started at or before age 4 yr, which is close to that noted in those with *LMNA* and *ZMPSTE24* mutations. However, patients with MDP have generalized loss of sc fat, especially evident in the older patients compared with those with *LMNA* and *ZMPSTE24* mutations. There is no radiological evidence of acroosteolysis and clavicular hypoplasia in MDP patients, whereas all MAD patients develop acroosteolysis by 2–4 yr of age. All males with MDP had hypogonadism and undescended testes, which were surgically removed in three of the patients and treated by orchidopexy in one patient.

Most interestingly, all MDP patients developed sensorineural hearing loss during childhood, which is not a feature of MAD patients with *LMNA* and *ZMPSTE24* mutations. Interestingly, mild sensorineural hearing deficit was reported on audiological examination in patients with Hutchinson-Gilford progeria syndrome (14) who harbor heterozygous c.1824C>T *LMNA* mutation. We have reported sensorineural hearing loss in a pedigree with atypical progeroid syndrome due to heterozygous p.P4R *LMNA* mutation (15), and Rankin *et al.* (16) reported it in a 20-yr-old female with type 2 diabetes and heterozygous p.R644C *LMNA* mutation, but her mother who carried the same mutation did not have it. However, hearing loss is not an accompanying feature of other laminopathies (17).

Interestingly, none of the patients with MDP had alopecia and/or sparse, thin hair seen in the other varieties of MAD (Supplemental Table 1). Other interesting features

include the presence of corneal opacities and dry eyes in MDP patients, presumably due to exophthalmos and exposure keratitis requiring surgery in two patients. We also observed extremely long eyelashes in three patients, but it is unclear at this time whether these findings are characteristic feature of MDP syndrome.

MDP patients seem to have better long-term survival than patients with MAD due to *LMNA* and *ZMPSTE24* mutations. All MDP patients are alive despite morbidities such as diabetes mellitus, hypertriglyceridemia, low high-density lipoprotein cholesterol, nonalcoholic steatohepatitis, and coronary artery disease. The oldest patient is 63 yr old. On the other hand, two patients with MAD due to *LMNA* mutations died at the young age of 10 and 16 yr and three with *ZMPSTE24* mutations have died at the ages 2, 27, and 37 yr.

In conclusion, patients with MDP-associated lipodystrophy constitute a novel syndrome whose genetic basis remains to be elucidated.

Acknowledgments

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