CLINICAL REPORT

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Mandibuloacral Dysplasia Type A in Childhood

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Mandibuloacral dysplasia type A (MADA) is characterized by growth retardation, postnatal onset of craniofacial anomalies with mandibular hypoplasia, progressive acral osteolysis, and skin changes including mottled pigmentation, skin atrophy, and lipodystrophy. Owing to its slowly progressive course, the syndrome has been recognized in adults, and pediatric case reports are scarce. We present the clinical case of two children in whom the diagnosis of MADA was made at an unusually early age. A 5-year-old boy presented with ocular proptosis, thin nose, and short and bulbous distal phalanges of fingers. A 4-year-old girl presented with round face and chubby cheeks, thin nose, bulbous fingertips, and type A lipodystrophy. In both, a skeletal survey showed wormian bones, thin clavicles, short distal phalanges of fingers and toes with acro-osteolysis. Both children were found to be homozygous for the recurrent missense mutation, c.1580G>A, (p.R527H) in exon 9 of the *LMNA* gene. Thus, the phenotype of MADA can be manifest in preschool age; diagnosis may be suggested by short and bulbous fingertips, facial features, and lipodystrophy, supported by the finding of acral osteolysis, and confirmed by mutation analysis.

Key words: *LMNA*; MADA; mandibuloacral dysplasia; mandibuloacral dysplasia type A; bulbous fingertips; acro-osteolysis; type A lipodystrophy

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INTRODUCTION

Mandibuloacral dysplasia type A (MADA; OMIM# 248370) is an autosomal recessive disorder characterized by growth retardation, postnatal onset of craniofacial anomalies with mandibular hypoplasia, skeletal abnormalities with progressive distal phalanges, and clavicular osteolysis, in addition to skin changes like mottled pigmentation and atrophy [Young et al., 1971; Freidenberg et al., 1992; Tudisco et al., 2000; Simha and Garg, 2002]. Some patients show progeroid (premature aging) features such as thin nose, sparse, brittle hair, and sclerodermatous (stiff and parched) skin. Among other typical features we can find lipodystrophy and metabolic complications due to insulin resistance and diabetes [Freidenberg et al., 1992]. Lipodystrophy type A is characterized by a marked acral loss of fatty tissue, with normal or heightened presence of such tissue in the neck and trunk. This pattern is similar to that described in patients with Dunningan-type familial partial lipodystrophy (FPLD2; OMIM# 151660). MADA, as FPLD2, is caused by mutations in the *LMNA* gene (*LMNA*; OMIM# 150330) encoding the A and C lamins, intermediate filaments of the nuclear

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envelope. The most common MADA defect is a homozygous missense mutation (p.R527H) in the C-terminal domain of lamins A/C [Novelli et al., 2002; Shen et al., 2003], but different homozygous or compound heterozygous patients have been reported [Cao and Hegele, 2003; Plasilova et al., 2004; Garg et al., 2005; Kosho et al., 2007; Lombardi et al., 2007; Agarwal et al., 2008; Zirn et al., 2008].

MAD patients characterized by generalized lipodystrophy (type B) (MADB; OMIM# 608612) affecting the face as well as extremities and severe progressive glomerulopathy showed compound heterozygous mutations in the *ZMPSTE24* gene encoding a zinc metalloproteinase involved in post-translational proteolytic cleavage of carboxy terminal residues of farnesylated prelamin A to form mature lamin A [Agarwal et al., 2003].

The rarity of the MADA condition, which has predominantly come to light in the Lazio area, a region of Italy, makes the identification of the phenotype complicated, but the clinical aspects are recognizable in preschool age and become more severe with increasing age; we describe the youngest patients in the literature, underlining the clinical features in pediatric age.

MATERIALS AND METHODS

DNA Isolation

Genomic DNA was extracted from whole blood samples using EZ1 DNA Blood kit (Qiagen, Hilden, Germany) and BioRobot EZ1 instrument (Qiagen).

Mutational Analysis

The coding exons of the *LMNA* gene, including the splice junctions, were amplified by PCR with modified primers (*LMNA* Gene Amplification Kit, Diatheva SRL, Fano, Italy). The amplicons have been analyzed by direct sequencing with M13 universal primers using 3130xl Genetic Analyzer (Life Technologies Corporation, Foster City, CA).

CLINICAL REPORTS

Patient 1

The boy is the first child of healthy nonconsanguineous parents with negative family history. The father's height was 180 cm and the mother's height 158 cm. He was born at term by spontaneous delivery. Birth weight was 2,970 g (10th–25th centile), length 49 cm (10th–25th centile). Psychomotor development was normal. He was referred to our Pediatric Department for assessment at the age of 5 years and 3 months because of bulbous distal phalanges of fingers. Head circumference was 51.5 cm (50th–75th centile), height 106.4 cm (25th centile), and weight 14 kg (3rd centile); the pubertal stage was A0P1B1, testes were 1–2 ml bilaterally.

He had ocular proptosis, a thin nose, prominent cheeks, slight micrognathia, malocclusion with overlapping teeth, thin skin with slightly prominent veins on the trunk, lipodystrophy type A, with an acral loss of fatty tissue, also evident on the shoulders, thin clavicles, hypermobile shoulders, and prominent shoulder blades (Fig. 1A). He had short and broad distal phalanges without nail anomalies (Fig. 1B). We found hyperpigmented skin spots, like freckling, on the groin and underarm areas and in the latter part on a background of hypopigmentation (Fig. 1C). Investigations including thyroid function, celiac markers, total cholesterol, HDL cholesterol, LDL cholesterol, ApoA-I, ApoB, liver enzymes, triglycerides, insulin, uric acid, and HBA1c were all normal. Skeletal survey showed normal skull thickness with wormian bones (Fig. 1D), normal spine without vertebral sclerosis (Fig. 1F), slightly thin ribs, normal pelvis, thin clavicles (Fig. 1E), short terminal finger, and toe phalanges with acro-osteolysis (Fig. 1G,H). At the chronological age of 4 years and 2 months, the bone age was 2 years and 6 months in the phalanges and 2 years and 8 months in the wrist (Greulich and Pyle atlas). Bone densitometry showed vertebral bone density under the 1st centile.

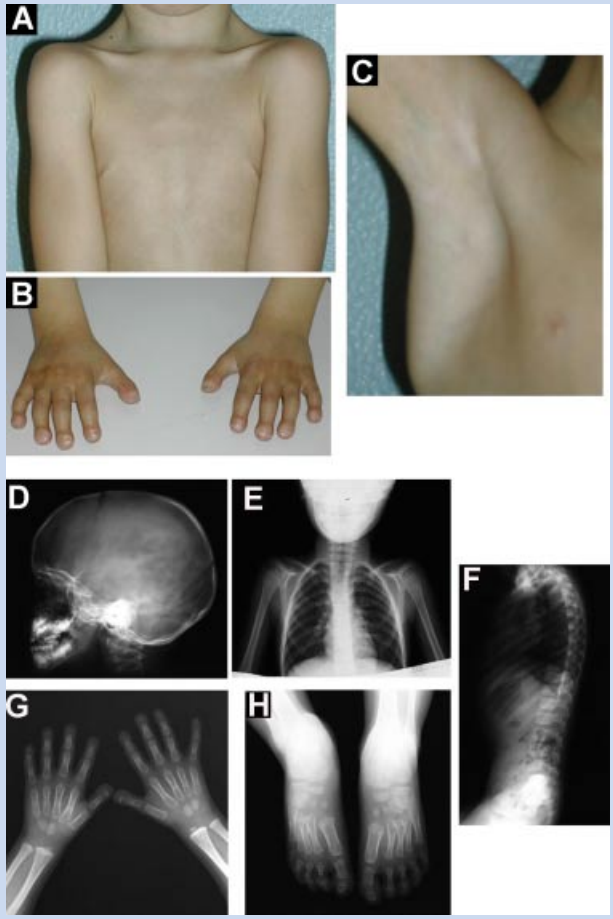

FIG. 1. Patient 1. A: Thin skin with slightly prominent veins on the trunk, thin clavicles, hypermobile shoulders, and prominent shoulder blades. B: Hands—short and broad distal phalanges without nail anomalies. C: Hyperpigmented skin spots, like freckling, on the groin and underarm areas and in the latter part on a background of hypopigmentation. D: X-Rays of the skull—wormian bones. E: X-rays of the thorax—slightly thin ribs, thin clavicles. F: Vertebral X-rays—normal spine. G: X-rays of the hands—short terminal finger phalanges with acro-osteolysis. H: X-rays of the feet—short terminal toe phalanges with acro-osteolysis. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Patient 2

She is the first female born at term of gestation to healthy consanguineous parents (first cousins) from Pakistan. The father's height was 185 cm and the mother's height 155 cm. A maternal uncle, son of consanguineous parents, and a paternal first cousin were reported to have short stature, digital anomalies, difficulty in bending their legs and in sitting down (they were not examined). The girl was born at term, but further information on birth weight, length, and head circumference was not available. When brought to us at the age of 4 years and 2 months, her head circumference was 48 cm (3rd centile), height 97 cm (25th–50th centile), and weight 16 kg (50th centile). Pubertal stage: A0P1B1. She had a round face and chubby cheeks (Fig. 2A), a thin nose, prominent cheeks,

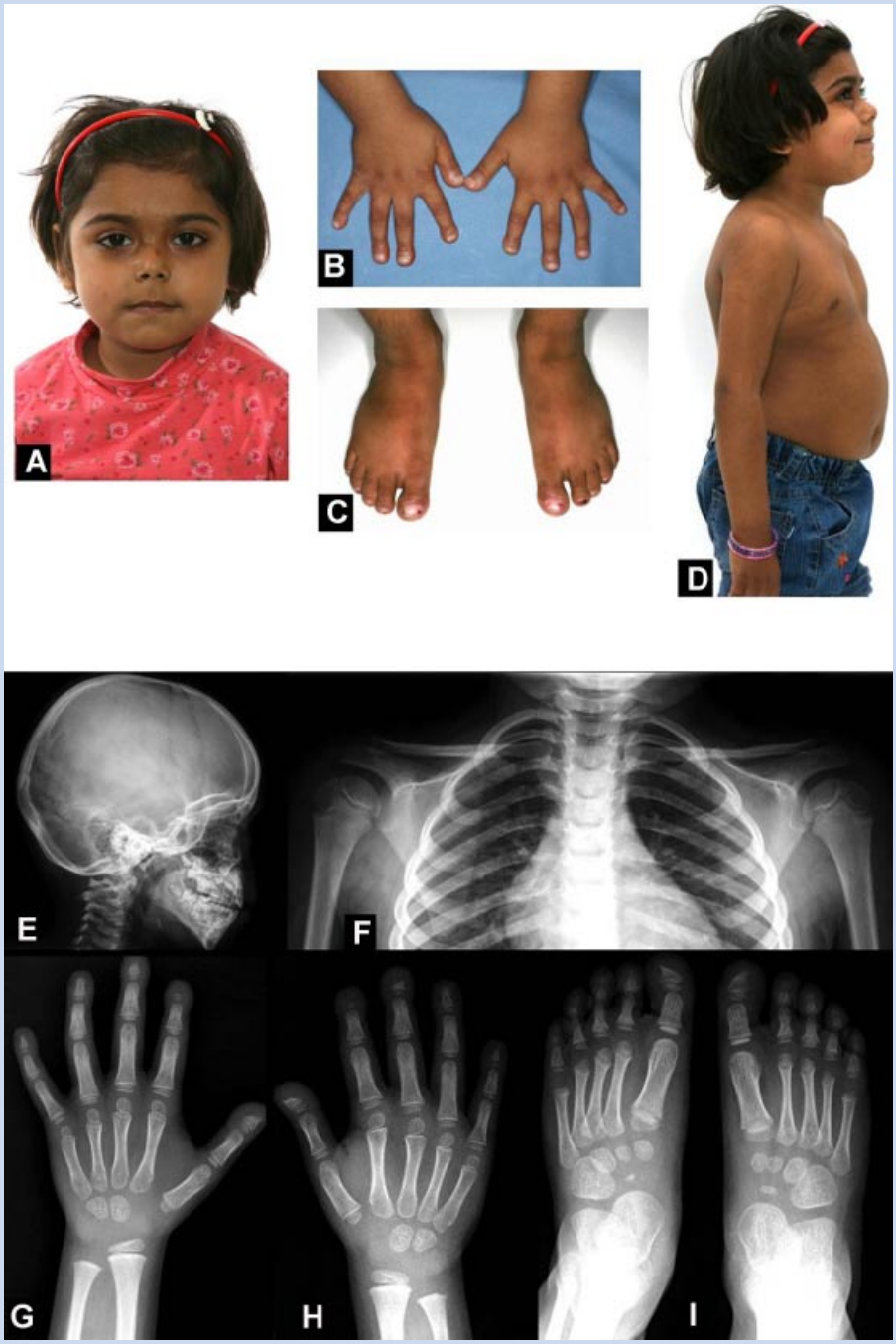

FIG. 2. Patient 2. A: Round face and chubby cheeks. B: Hands: short and broad distal phalanges with short nails. C: Feet: broad first toe. D: Prominent abdomen and subcutaneous fat more evident on trunk and abdomen. E: X-rays of the skull—wormian bones. F: X-rays of the thorax—thin clavicles. G–I: Hands and feet X-rays showed short terminal finger and toe phalanges with acro-osteolysis.

lipodystrophy type A with prominent abdomen, and subcutaneous fat more evident on trunk and abdomen than on limbs and an acral loss of fatty tissue (Fig. 2D). She had short and broad distal phalanges with short nails and broad first toe (Fig. 2BC). Her psychomotor development was normal. Skeletal survey showed wormian bones (Fig. 2E) and thin clavicles (Fig. 2F). Hand and feet X-rays showed short terminal finger and toe phalanges with acro-osteolysis (Fig. 2G–I). Skeletal age corresponded to her chronological age. Investigations including thyroid function, celiac markers, total cholesterol, HDL cholesterol, LDL cholesterol, liver enzymes, triglycerides, glycemia, and insulin were all normal.

RESULTS

Both affected subjects were homozygous for the c.1580 G → A transition in exon 9 resulting in substitution of arginine with histidine at 527 codon (p.R527H) (Fig. 3). This missense mutation was present in a heterozygous state in all four clinically unaffected parents.

DISCUSSION

MADA is a specific genetic entity which belongs to a group of genetic disorders, known as "primary laminopathies" among which can be found a neuropathy, muscular dystrophies, cardiomyopathies, lipodystrophies, and progeroid disorders [Broers et al., 2006; Burke and Stewart, 2006; Capell and Collins, 2006; Jacob and Garg, 2006; Liu and Zhou, 2008]. Given the rarity of MADA, it is of vital importance to be able to know and recognize the clinical signs in pediatric age in order to be in a position to suspect the diagnosis. Our patients presented the following clinical features which should be highlighted: slightly prominent eyes and prominent cheeks, thin acral subcutaneous fatty tissue also evident on the shoulders, visible veins on the trunk, skeletal anomalies with wormian bones, increased shoulder mobility with thin clavicles, acro-osteolysis. Patient 1 also showed slight mandibular hypoplasia and tooth anomalies, with malocclusion and overlapping teeth, hyperpigmented skin spots, like freckling, on the groin and underarm areas and in the latter part on a background of hypopigmentation. The only element different in our first patient that differed from the literature relates to the thinness of the subcutaneous tissue located in the area of the upper trunk, in particular around the shoulders.

These features, which are evident in the review of the literature reported in Table I, are typical of MADA caused by the p.R527H mutation in the *LMNA* gene. Other MADA mutations cause different phenotypes. The homozygous *LMNA* mutation p.K542N, reported by Plasilova et al. [2004], is associated with more severe progeroid features and the investigators diagnosed the patients as having Hutchinson–Gilford Progeria Syndrome (HGPS; OMIM# 176670). The homozygous p.A529V described by Garg et al. [2005] in two Turkish patients also causes variations in the MADA phenotype. Progeroid appearance, hypoplastic mandible, acro-osteolysis, partial loss of subcutaneous fat, associated to absence of clavicular dysplasia, normal metabolic profiles, muscle hyposthenia, and generalized hypotonia were reported in a 27-year-old Italian woman compound heterozygous p.R527H/p.V440M [Lombardi et al., 2007]. Similar phenotype combining mandibuloacral dysplasia (MAD), progeroid appearance, and rigid spine muscular dystrophy was caused by the p.R471C homozygous mutation in *LMNA* [Zirn et al., 2008]. A 56-year-old Japanese woman with MAD, type A lipodystrophy and severe progressive skeletal changes showed the homozygous p.A529T mutation [Kosho et al., 2007]. Cao and Hegele [2003] reported heterozygous mutations p.R527C/p.R471C in a female who initially was thought to have atypical HGPS. Recently, homozygous p.R527C mutation was found to be associated with early and severe presentation of typical MAD features [Agarwal et al., 2008]. The onset of mandibular and clavicular hypoplasia, acro-osteolysis, and lipodystrophy of the limbs during infancy is comparable to that of which we observed in our young patients. Moreover, we documented that bone resorption observed in our young first MADA patient is mediated by induction of high levels of matrix metalloproteinase

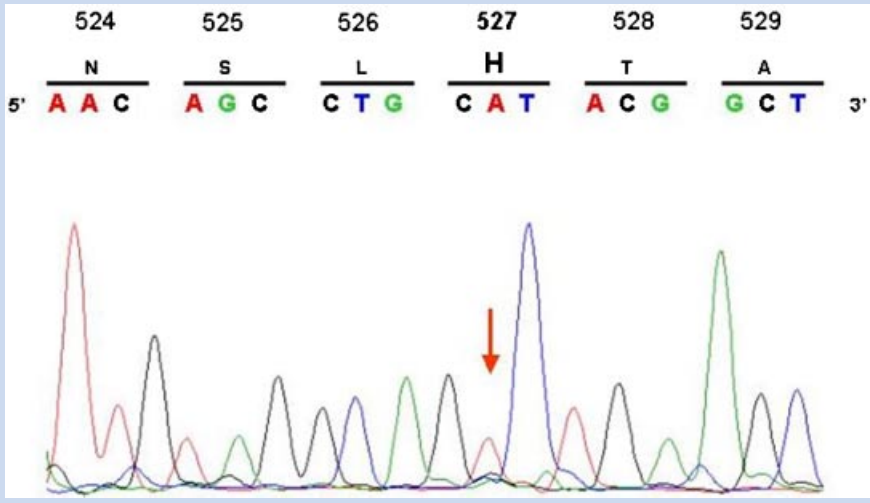

FIG. 3. Molecular analysis of the *LMNA* gene demonstrated the homozygous p.R527H mutation in exon 9 of the gene in both patients. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE I. Clinical Features and Review of the Literature

Reference	Novelli et al. [2002]									Shen et al. [2003]	Simha et al. [2003]			Lombardi et al. [2008]	Case 1	Case 2	Total
Gender	M	F	F	M	F	M	F	M	M	M	F	F	M	F	M	F	8 M/8 F
Age	35	20		50						12	20	16	12	27	5	4	
Postnatal growth retardation	+	+	+	+	+	+	+	+	+	?	+	+	−	−	−	−	11/15
Craniofacial																	
Prominent eyes	+	+	+	+	+	+	+	+	+	+	+	+	−	?	+	−	13/15
Beaked nose	+	+	+	+	+	+	+	+	+	+	+	+	?	+	−	−	13/15
Prominent cheeks	+	+	+	+	+	+	+	+	+	+	?	?	?	+	+	+	13/13
Dental overcrowding	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	14/16
Micrognathia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	15/16
Skeletal																	
Delayed closure of cranial sutures	+	+	+	+	+	+	+	+	+	+	—	—	?	?	−	−	10/14
Wormian bones	+	+	+	+	+	+	+	+	+	+	?	?	?	?	+	+	12/12
Mandibular hypoplasia	+	+	+	+	+	+	+	+	+	?	+	+	+	+	+	−	14/15
Acro-osteolysis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	16/16
Clavicular dysplasia/ osteolysis	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	14/16
Narrowing sloping shoulders	+	+	+	+	+	+	+	+	+	+	?	?	?	?	+	−	11/12
Joint contractures/stiffness	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	14/16
Skin																	
Partial lipodystrophy (type A)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	16/16
Mottled cutaneous pigmentation	+	+	+	+	+	+	+	+	+	+	+	+	+	?	+	−	14/16
Acanthosis nigricans	+	+	+		+	+	+	+	+	+	+	+	?	?	−	−	12/14
Alopecia	+	−	−	+	−	+	−	+	+	?	−	?	?	?	−	−	5/12
Other clinical features														Hypotenia, hypostenia			
Mutation	R527H R527H	R527H R527H	R527H R527H	R527H R527H	R527H R527H	R527H R527H	R527H R527H	R527H R527H	R527H R527H	R527H	R527H R527H	R527H R527H	R527H R527H	R527H V440M	R527H R527H	R527H R527H	

9 (MMP-9) active form in serum sample such as in older patients (data not shown) [Lombardi et al., 2008].

The cases reported here indicate that MADA may be clinically manifest already in preschool children. Telltale features may be ocular proptosis, micrognathia, and short bulbous distal phalanges. This last feature is the most striking one, followed by the thinning of the skin on the nose with thinning of nasal bridge and ridge. So one simply has to think about MAD, also in childhood, when one sees the bulbous fingertips. Radiographic examination of the hands and clavicles may confirm the presence of thinning of the lateral one-third of the clavicles and osteolysis, which is most prominent in the distal phalanx of the second finger and mutation analysis of *LMNA* may confirm the diagnosis.

The most important differential diagnosis involves HGPS. The classical form is more easily recognizable, while several nonclassical forms may be confused with MADA, since they share some features like progressive distal phalanges and clavicular osteolysis. Nevertheless, in HGPS patients show the first clinical signs in their early years, with growth retardation, short stature, low weight, alopecia, and thin eyebrows. It has been noted that in MADA clinical signs are evident from 4 years of age and growth retardation is less evident. Moreover, the facial clinical features, although similar to those found in HGPS, are decidedly less marked. Hair may be thin and sparse but alopecia is in general less evident and less precocious. Tooth anomalies are different, with missing teeth in HGPS and overcrowding of teeth in MADA. Lipodystrophy is generalized in HGPS, while MADA patients show lipodystrophy type A with a marked acral loss of fatty tissue, with normal or heightened presence of such tissue in the face, neck, and trunk. MAD patients characterized by generalized lipodystrophy (type B) (MADB; OMIM# 608612) affecting the face as well as extremities and severe progressive glomerulopathy showed compound heterozygous mutations in the *ZMPSTE24* gene. The most important clinical feature in HGPS is heart attack, which is one of the most common causes of death, while in MADA the main problem is insulin-resistant diabetes.

The correct diagnosis is important not only for prognosis and genetic counseling but also for the potential early introduction of therapeutic measures in the future, such as those aimed at inhibiting bone resorption.

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