Mandibuloacral Dysplasia with Type A Lipodystrophy (MADA) in A 16 year-old Iranian Girl

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Manuscript received: 02.09.15
Manuscript accepted: 09.10.15

Abstract

MADA is a rare syndrome characterized by premature aged appearance, and variety of abnormalities involving bone development, skin coloring (pigmentation), and fat distribution. the disease resulting from mutation of LMNA gene. Here we report a 16 year-old girl with joint deformities especially in the fingers & loss of fatty tissue under the skin (progeroid feature). Based on these finding MADA was suspected and LMNA gene sequencing was performed revealing a homozygous mutation in R527H.

Key words: LMNA, mandibulo acral dysplasia, lipodystrophy, R527H
Introduction

Mandibulo acral dysplasia with type A lipodystrophy (MADA: OMIM # 24570) is rare autosomal recessive disease. It was described initially by Cavallazzi & colleagues as an atypical form of cleidocranial dysostosis. More than 100 patients with this disorder have been reported up to now.

Its most common features are postnatal growth retardation, skeletal abnormalities such as hypoplasia of mandible and clavicle, acroosteolysis of terminal phalanges, delay closure of cranial suture, joint contracture, lipodystrophy limited to extremities. Affected individuals may also present progeroid features such as bird-like face with micrognathia, pinched nose, prominent eyes, scleroderma-like skin changes, & nail dysplasia. Metabolic abnormalities such as insulin resistance diabetes and hyper-triglyceridemia can be seen [1].

Case report

Sixteen-year-old girl referred to our center for progerid facies & joint contracture. She is the fourth child of healthy and unrelated parents. There was no similar case in her family. She was born by cesarian section at term gestational age. Birth weight, length, and head circumference were: 2800 gr, 47 cm, and 34 cm respectively (on 25th percentile). Pregnancy and delivery were uneventful. Growth and development were normal up to three-year-old of age when developed brownish skin pigmentation on the flank and knee that progressed to all parts of the body and then gradually developed limitation of motion in elbow, hip, and muscle stiffness.

Puberty was at thirteen-year-old except breast development that was not good up to now. One year ago had operation because of rupture of hemorrhagic cyst in left ovary. In physical examination at sixteen years her weight is 35 kg (below 3rd percentile) and height was 155 (3rd percentile).

Positive findings are: generalized loss of subcutaneous fat, skin was taut, dry and erythematous associated with contracture of metacarpal and metatarsal joints. She has a large head, prominent eyes, micrognathia, thin beak-like nose with alar hypoplasia, prematurely aging appearance.
dystrophic nail, thin mottled hyper pigmented skin mostly in groin and axila thining and atrophy of the skin, prominently visible and superficial vasculature (figure 1,2,3,4 and table 1)

Table -1: Clinical and Laboratory Feature of the Presented Patient with MADA

<table>
<thead>
<tr>
<th>Micrognathia</th>
<th>Generalized lipodystrophy</th>
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<tbody>
<tr>
<td>Beaked like nose</td>
<td>Skin atrophy</td>
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<tr>
<td>Prominent eye</td>
<td>Mottled cutaneous pigmentation</td>
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<td>Joint contracture</td>
<td>Joint contracture</td>
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<td>Clvaicular hypoplasia</td>
<td>Hyperglycemia</td>
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<tr>
<td>Dystrophic nail</td>
<td>High triglyceride &amp; Cholesterol level</td>
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Figure 1- Micrognathia, Beaked nose and Skin pigmentation can be seen
Figure 2-Dystrophic nail, Superficial vasculature and loss of skin fat

Figure 3 –Loss of skin fat, Clinodatly, Visible and Superficial Vasculature, Joint Contracture
Lab test

All test including CBC, thyroid function test, hormone study (FSH, LH, prolactin, progesterone) was normal, but triglyceride, cholesterol, FBS were high (229, 210, 117 respectively)

Skin biopsy at six-year-old of age: dyskeratosis congenita
Sequencing was done showed: homozygous mutation as R527H

Discussion

Mandibulo acral dysplasia with type A lipodystrophy is a very rare syndrome characterized by premature aged appearance, and bone abnormalities. It caused by homozygous or compound heterozygous mutation in gene encoding nuclear laminar protein, lamin AC (LMNA).

Two types of mandibulo acral dysplasia have been identified type A and type B. Type A is caused by mutation of lamin A/C (LMNA) gene which maps to chromosome 1q21, and type B is caused by mutation of zinc metalloproteinase (ZMPSTE24) gene. Why these different disorders arise from mutation in the same gene yet remain to be determined.
Disease caused by LMNA mutation (MAD, Dunningan-type familial partial lipodystrophy, Charcot-Marie-Tooth type 2B, autosomal dominant and autosomal recessive Emery-Dreifuss muscular dystrophy, Limb-Girdle muscular dystrophy type 1B, Hutchinson-Gilford progeria) provide a further and more dramatic example of this phenomenon as all manifest separate and distinctive phenotypic feature including skeletal changes, skin finding, lipodystrophy, cardiomyopathy, muscular dystrophy, and neuropathy [3, 6, 8, 9, 10, 12].

Although the wide ranging phenotypes of laminopathies result from LMNA mutation that occur through out of the gene, a different scenario is emerging with MADA. The arginine at position 527 isolated within c-terminal immunoglobulin-like domain in the center of beta sheet on the domain surface. Mutation at this site are postulated to disturb protein structure [14, 10]. Substituting a prolin in this location (R527P) result in autosomal dominant Emery-Dreifuss with some but not all patient with lipodystrophy. [4, 5, 1, 13] Substituting a histidine in this position (R527H) has been showed in mandibuloacral dysplasia with type A lipodystrophy. There is a very specific genotype-phenotype correlation between this exact aminoacid substitution and characteristic constellation of lipodystrophy with skeletal and skin manifestation in this rare disease. Among approximately 100 patient with MADA reported up to now there is a certain degree of phenotypic variability for example in our patient lacked alopecia, tooth loss, hearing loss and she had involvement of ovary (hemorrhagic cyst) that was not reported in literature.

References


