A 3-Year-Old Boy with Severe Obesity and Pseudoacromegaly; Short course treatment with Orlistat™

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Abstract

Specific syndromes and single-gene defects are rare causes of obesity, accounting for less than one percent of childhood obesity. Most endocrine and genetic causes of obesity are associated with short stature. The purpose of this paper was clinically and biochemically describe a toddler with insulin mediated pseudoacromegaly and in addition, to examine the response to pharmacologic therapy. The patient was a 3-year-old boy with severe obesity, pseudoacromegaly, Blount disease and acanthosis nigricans diagnosed as insulin resistance syndrome according to clinical and biochemical findings. A trial for measuring the effect of Orlistat™ on weight gain and body mass index was done.

Keywords: Childhood obesity, Hereditary insulin resistance syndrome, Pseudoacromegaly, Body Mass Index

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Introduction
The study of childhood obesity has continued to grow exponentially in the recent decades (1). Some specific syndromes and single-gene mutations which are linked to obesity in childhood have been identified. These are rare causes of obesity, responsible for less than one percent of childhood obesity in tertiary care centers (2, 3). Exogenous obesity drives linear height, so most obese children are tall for their age. By contrast, most endocrine and genetic causes of obesity are associated with short stature (4). In this paper we report a 3-year-old boy with severe obesity, pseudoacromegaly and acanthosis nigricans diagnosed as insulin resistance syndrome according to clinical and biochemical findings. A trial for measuring the effects of Orlistat™ on weight gain and BMI was performed.

Case presentation
A 3-year-old boy presented with severe obesity and tall stature. The patient was born of a full-term pregnancy with spontaneous vaginal delivery to healthy related parents of Persian origin. He weighed 3,700 g and heighted 54 cm at birth and was hospitalized for 4 days for the neonatal hyperbilirubinemia. He was presented with progressive growth rate that persuaded medical attention at the age of 12 months. At that time he has had polyphagia and severe weight gain but biochemical evaluations were unspecific (Table 1). At 37 months of age, he was referred to us because of polyphagia; severe obesity and abnormal rapid growth. Physical examinations revealed generalized obesity, coarse facial feature, cutis verticis gyrata, thick skin and severe acanthosis nigricans at neck and axillary regions. Systolic and diastolic blood pressures were at 86th and 95th percentiles for age, respectively. His height was 110 cm (Z-score: 3.4, percentile: 99.9) (5); his weight 50 kg and his BMI was 41.3 (Z-score: 7.2) (6). Characteristic findings of genetic syndromes associated with obesity including dimorphic features, short stature, developmental delay or mental retardation, retinal changes and deafness were negative (7-9). Tibia vara was characterized in patient by progressive bowed legs and tibial torsion that was compatible with Blount disease.

Drug and habitual history was unspecific. Family history was positive for overweight and acanthosis nigricans in his two sisters and obesity, irregular menses and infertility in his aunt. His mother has had eclampsia in her previous pregnancy and her neonate died at the age of 2 days. Laboratory data revealed insulin resistance according to HOMA index (Table 1). Bone age estimated 4 years by assessing the hand-wrist radiograph. The patient referred to an orthopedic surgeon for management of Blount disease and was candidate for surgery because of progressive bowing. Lifestyle interventions and an appropriate weight-loss program were recommended to his family. But his physical activity was limited more and more and the mother was unable to control his weight gain with diet alone. Informed consent was taken from his parents for pharmacologic therapy.

Response to pharmacologic Therapy and Follow-up
The patient was treated with Orlistat™ 120 mg three times daily (taken with meals). Supplemental multivitamin administered too. The patient followed for 9 months and monitored for side effects, intolerance to drug and response to therapy by measuring weight, height and BMI (Figure 1). This course of therapy was safe without any side effects.
<table>
<thead>
<tr>
<th>Age (months)</th>
<th>References</th>
<th>12 months</th>
<th>37 months</th>
<th>43 months</th>
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<td></td>
<td>10</td>
<td>50</td>
<td>53</td>
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<td>Height (cm)</td>
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<td></td>
<td>110</td>
<td>112</td>
<td>115</td>
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<tr>
<td>Fasting blood sugar (mg/dL)</td>
<td></td>
<td>70 – 100</td>
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<td>Urea nitrogen (mg/dL)</td>
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<td>(7.0-18.0)</td>
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<tr>
<td>Creatinine (mg/dl)</td>
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<td>(0.1-0.5)</td>
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<tr>
<td>Calcium (mg/dl)</td>
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<td>9</td>
<td></td>
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<tr>
<td>Phosphorus (mg/dl)</td>
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<td>4.7</td>
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<td>Aspartate transaminase (U/L)</td>
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<td>Alanine transaminase (U/L)</td>
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<td>Alkaline phosphatase (u/liter)</td>
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<td>T4 (µg/dL)</td>
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<td>10.3</td>
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<td>T3 (ng/dL)</td>
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<td>TSH(µu/mL)</td>
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<td>Parathyroid hormone (pg/ml)</td>
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<td>Growth Hormone (ng/mL)</td>
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<td>90</td>
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<td>120</td>
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<td>Base-line Cortisol level(µg/dL)</td>
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<td>Insulin growth factor-I (ng/mL)</td>
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<td>(27.4-113.5)</td>
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<td>Leptin (ng/mL)</td>
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<td>Insulin (micIU/mL)</td>
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<td>5</td>
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<tr>
<td>QUICKI</td>
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<td>0.3041</td>
<td></td>
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<tr>
<td>Aldolase (U/L)</td>
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<td>(Up to 7.6)</td>
<td>8</td>
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</table>

- HOMA IR is calculated using the following formula: (fasting insulin [micU/ml]) (fasting glucose [mmol/L]/22.5). Insulin resistance is defined as HOMA-IR>2 (Reference 13).
- QUICKI can be calculated using the following formula: 1/[(Log[fasting insulin (micU/ml]+Log(fasting glucose [mg/dl])); impaired is defined as QUICKI <0.339 (Reference 13).

**Figure 1- Weight, height and BMI before and after treatment with Orlistat™. The patient was treated with Orlistat™ 120mg three times daily for 9 months.**
Discussion

The presented patient had severe obesity, pseudoacromegaly and insulin resistance. Most of the syndromal causes of obesity in children are associated with cognitive or developmental delay. Different genetic syndromes associated with obesity in children such as Albright hereditary osteodystrophy with short stature and mild cognitive deficit, Alstrom-Hallgren with blindness and deafness and central obesity, Bardet-Biedl with mental retardation, deafness and central obesity, Carpenter with short stature and Prader-willi with short stature and cognitive deficit were ruled out in this patient. The age of onset is helpful in distinguishing over-feeding from hereditary causes of overweight since syndromal overweight often has onset before two years of age (7-9). The onset of obesity in this patient was in the first six months of age. Stature is useful in distinguishing exogenous obesity from that secondary to genetic or endocrine causes. Despite short stature with most endocrine and genetic causes of obesity, linear and acral growth is usually accelerated in insulin resistance syndrome and may present as pseudoacromegaly. In this patient, according to suppressed GH level after an Oral Glucose Tolerance Test (OGTT) and normal Insulin growth factor–I (Table1) acromegaly was ruled out.

Examination of the skin and hair is particularly useful in evaluating signs of endocrine etiologies in obese patients. Acanthosis nigricans may signify type 2 diabetes or insulin resistance (10-13). Positive family history of overweight and acanthosis nigricans in his two sisters and obesity, irregular menses and infertility in his aunt and obesity, acanthosis nigricans and pseudoacromegaly were found in this patient which was compatible with pediatric features of insulin resistance syndrome.

His HOMA.IR values was 5 and 4.5 in two separate evaluations and QUIKI test was impaired, both two reveal insulin resistance (Table1). Hyperinsulinemia promotes linear growth by activating skeletal IGF–I receptors and low levels of IGFBPs can promote IGF–I action by allowing it to be freely and metabolically available. Increased IGF–I / IGFBP–1 ratios are presumed to result in the development of acanthosis nigricans (14).

Melanocortin receptor 4 haploinsufficiency carriers have hyperphagia and hyperinsulinemia (which is most pronounced in patients younger than 10 years of age), higher than average bone mineral density and more rapid linear growth than BMI-match controls. It has been suggested that MC4R mutations constitute the most common monogenic cause of human obesity with up to 4% of all patients with morbid obesity attributable to mutations in this gene. Leptin levels, lipid profile, adrenal function, resting metabolic rate, thyroid function and reproductive function were all normal in these mutation carriers. Subjects who are homozygous for MC4R have a greater average body mass index than heterozygous carriers of the mutation (15, 16). Then according to his features, MC4R insufficiency may consider as a plausible diagnosis for our patient.

Among orthopedic co-morbidities of obesity, this patient has tibia vara (Blount disease). It results from inhibited growth of the medial proximal tibial growth plate due to excessive abnormal weight bearing. For treating this condition, we referred him to an orthopedic surgeon for management. An appropriate weight loss program (for prompt and sustained weight reduction to prevent recurrence) should be considered in this situation. Because the lack of compliance to restrictive diet and physical activity, as has been showed in previous studies, it was difficult to determine the best treatment for this patient (6). As other investigators concluded, short term treatment with OrlistatTM in the context of a behavioral program is a well-tolerated treatment modality and has a side-effect profile similar to that observed in adults (17-19). According to these trials, this patient also treated with OrlistatTM for nine months. Despite any decrease in body mass index in this patient, the rate of weight gain was lower in comparison with the period of non-pharmacological management. This course of treatment was safe and without any side-effect.

Acknowledgements

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References
5. LMS Parameters for Boys: Height for Age. National health and nutrition survey (NHANES), CDC/National Center for Health Statistics.
6. LMS Parameters for Boys: BMI for Age. National health and nutrition survey (NHANES), CDC/National Center for Health Statistics.