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Caloric restriction in Alström syndrome prevents hyperinsulinemia

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Abstract

Alström syndrome (AS; MIM 203800) is an autosomal recessive disorder characterized by cone-rod dystrophy, dilated cardiomyopathy, sensorineural hearing impairment, developmental delay, and most case had both childhood-onset obesity and hyperinsulinemia. Currently, the pathogenesis of this disease is not clear. Here we report an 18-month-old boy with Alström syndrome. He had obesity but with normal insulin and glucose levels. Molecular analysis of the *ALMS1* gene revealed a homozygous deletion 11116_11134 del n(19) in exon 16. His body mass index decreased from 25.0 to 20.7 after calorie restriction for 9 months, and his insulin and glucose levels remained normal. Finding in this case suggests that hyperinsulinemia is a secondary event in Alström syndrome, and early-commenced treatment prevents hyperinsulinemia.

Keywords

Alström syndrome; *ALMS1*; obesity; hyperinsulinemia; calorie restriction

Introduction

Alström syndrome (MIM 203800) is a multisystemic autosomal recessive disorder characterized by cone-rod dystrophy, infantile-, adolescent-, or adult-onset dilated cardiomyopathy, progressive sensorineural hearing impairment, obesity, type 2 diabetes mellitus (type 2 DM), and developmental delay [Marshall et al., 2007a; Marshall et al., 2007b]. Until recently, more than 450 cases had been identified [Marshall et al., 2007a]. The gene *ALMS1*, encoding a ubiquitously expressed 461kD protein that localizes to the basal bodies of cilia, may play a role in intracellular trafficking [Hearn et al., 2005; Li et al., 2007; Marshall et al., 2007a]. Truncation of this protein in mouse results in stunted cilia on kidney epithelial cells, and reduced calcium influx in response to mechanical stimuli [Li et al., 2007].

However, the pathogenesis of Alström syndrome is still not clear. Although obesity would lead to insulin resistance [Martyn et al., 2008] and most patients with Alström syndrome had both obesity and hyperinsulinemia at diagnosis [Minton et al., 2006], hyperinsulinemia has been mentioned in patients as young as one year of age [Marshall et al., 2007a; Marshall et al., 2005]. Here we report an 18-month-old boy with Alström syndrome. He had typical clinical

manifestations of the disease, his insulin and glucose levels were normal at diagnosis, and were kept normal under calorie restriction.

Case Report

The Proband was an 18-month-old boy born to a healthy woman at 41 wks gestation following an uncomplicated pregnancy. He had normal birth weight (3,326 g). Obesity with weight exceeding the 97th centile was noted since two months of age (7.1 kg at 2 months old; 10.8kg at 4 months old; BMI was 24 at 5 months old). Dilated Cardiomyopathy was found at 4 months, with a left ventricle ejection fraction of 47.6%. Nystagmus was noted at age 5 months and cone-rod dystrophy was confirmed by electroretinography. Mild truncal hypotonia, delayed developmental milestones, hyperuricemia (uric acid 13.9 mg/dl), and frequent respiratory tract infection were also noted. His cardiac condition improved later and hyperuricemia resolved after stopping diuretics at one year of age. He had three hospitalizations before 9 months old due to respiratory tract infections.

Because Alström syndrome was clinically diagnosed in this patient, mutation analysis on the *ALMS1* gene was performed, as previously described [Marshall et al., 2007b]. In brief, primers were designed to amplify exon and exon-intron junctions. PCR amplification was adjusted and PCR products were purified and sequenced using an Applied Biosystems 3730xl DNA Analyzer (Applied Biosystems). Sequences were compared to *ALMS1* (GenBank NM_015120.4; AC074008.5) using MacVector TM 7.2.3 (MacVector Inc., Cary, NC). Nucleotide and amino acid numbering of mutation sites began at the start codon, ATG (Met) of the open reading frame [Marshall et al., 2007b]. The result revealed a homozygous deletion 11116_11134 del n(19) in exon 16. This mutation was previously described in another Taiwanese family [Marshall et al., 2007b].

Insulin measured at 5 months old was 11.9µU/mL (normal 5-20 µU/mL) when fasting blood glucose level was 94 mg/dL. Cholesterol (123 mg/dL), HDL (39 mg/dL), and triglyceride (53 mg/dL) levels were all normal. Calorie-restriction started after diagnosis at age 9 months. His body mass index improved at 18 months of age, although he was still over-weighted (13.9kg; 97th centile; BMI 20.67). He had normal glucose (89 mg/dL) and insulin (7.59 µU/mL) levels at that time. (Table 1)

Discussion

The *ALMS1* gene encodes a protein localized to the basal body of cilia [Hearn et al., 2005]. Several mammalian cell types, including neurons, have a single cilium [Satir 2007]. Mice with adult-specific knock-out of polycystin 1 A, a major ciliary signaling molecule have prominent phenotype – hyperphagia [Piontek et al., 2007; Satir 2007]. Mutations of the BBS protein resulted in defects in ciliary signaling and cause another obesity syndrome – the Bardet Biedl syndrome [Myktyyn and Sheffield 2004]. Obesity in these diseases may be related to the POMC neurons which are regulators of feeding behavior [Coll et al., 2004; Coll et al., 2007; Morton et al., 2006; Satir 2007]. Obesity phenotype can be generated by knocking out genes of the hypothalamic POMC neurons [Satir 2007]. Therefore, the elevated fasting serum glucose and insulin levels in the obese knock-out mice are likely to be secondary effects and they all disappeared in knockout animals whose dietary intake was strictly limited [Satir 2007].

The *Alms1*^{-/-} mice developed insulin resistance and increased body weight between 8 to 12 weeks of age, followed by hyperglycemia at approximately 16 weeks of age [Collin et al., 2005]. In patients, obesity occurs between 6-12 months; hyperinsulinemia has been noted between 1.5 and 4 years old (92%); while the onset of type 2 DM was at a median age of 16 years (82%). [Marshall et al., 2007a; Marshall et al., 2005]. Our patient is the youngest well-

documented case of Alström syndrome. During follow up, the left ventricular ejection fraction improved to 70% at his age of 11 months. However, visual impairment was still noted. The frequencies of bronchiolitis decreased after cautious hygiene care of the parents. He presented with obesity, but there was no hyperinsulinemia; hyperinsulinemia never appeared during the period under calorie restriction. Therefore early diagnosis and early treatment of patients with Alström syndrome is very important to prevent the development of hyperinsulinemia, insulin resistance and DM, in order to improve the outcome of the disease.

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TABLE 1

Age (month)	Body weight (kg)	Body height (cm)	Body mass index (kg/m ²)	Glucose (mg/dL)	Insulin (μU/mL)
2	7.1	59	20.4		
4	10.8	69	22.7		
5	11.9	69.9	24		
9*	13	76.6	25.0	94	11.9
12	13.9	80	21.7	79	7.79
18	13.9	82	20.7	89	7.59

* start calorie-restriction