Combined Occurrence of Alström Syndrome and Bronchiectasis

abstract

Alström syndrome (Online Mendelian Inheritance in Man ALMS #203800) is a rare hereditary disorder caused by mutations in the gene ALMS1. This rare disorder’s characteristics are cone-rod dystrophy resulting in blindness in childhood, insulin-resistant type 2 diabetes mellitus, truncal obesity, progressive sensorineural hearing loss, dilated cardiomyopathy, craniofacial features, hypothyroidism, elevation in liver transaminases, renal insufficiency, gonadal dysfunction, and menstrual irregularities. A 13.5-year-old girl was admitted to the hospital for complaints of excessive water consumption and urination over the previous 2 years. The patient’s parents were third-degree relatives. At physical examination, hyperpigmentation was present over the areola and acanthosis nigricans under the arms and on the neck. Audiologic examination revealed bilateral sensorineural hearing loss, and bilateral cataract was determined at ocular examination. The patient was monitored by the chest diseases department due to bronchiectasis. HbA1c was 13.1%. In mutation screening study, 2 novel mutations c.5586T>G; p.Tyr1862* and c.2905insT; p.L968fs*4 were detected in the ALMS1 gene. Saccharin test was positive. We emphasize that Alström syndrome may be complicated by bronchiectasis. Pediatrics 2014;133:e780–e783

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KEY WORDS
diabetes mellitus, Acanthosis nigricans, bronchiectasis

Drs Kaya and Çayır were responsible for manuscript preparation, data acquisition, and literature research; Drs Orbak and Döneray were responsible for manuscript editing; Dr Taşdemir was responsible for genetic analysis and manuscript editing; Dr Özantürk was responsible for genetic analysis; Dr Bingöl performed the nasal biopsy; Drs Kaya, Orbak, Çayır, Döneray, Taşdemir, and Bingöl were the patient’s doctors; and all authors approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2013-0284
doi:10.1542/peds.2013-0284
Accepted for publication Aug 19, 2013

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).
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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.
Alström syndrome (Online Mendelian Inheritance in Man ALMS #203800) is an autosomal recessive inherited disorder. It was first described in 1959 by Alström et al. Alström syndrome is characterized by cone-rod dystrophy resulting in blindness in childhood, insulin-resistant type 2 diabetes mellitus, truncal obesity, progressive sensorineural hearing loss, dilated cardiomyopathy, craniofacial features, hypothyroidism, elevation in liver transaminases, renal insufficiency, gonadal dysfunction, and menstrual irregularities. The ALMS1 gene is mapped to chromosome 2p13. Increased clinical interest and defined diagnostic criteria with improved genetic tests have led to a rapid increase in diagnosis over the past years; ~800 patients with Alström syndrome have been identified.

We report a patient with Alström syndrome with established bronchiectasis, which has not been reported in the literature, and poorly controlled diabetes at the time of diagnosis.

CASE REPORT

A 13.5-year-old girl was admitted to the hospital for complaints of excessive water consumption and urination over the previous 2 years. The patient’s parents were third-degree relatives. She has a healthy brother. Her other brother died of uncertain cause at 6 months of age. In her history, she had received occasional treatment of cough and had been monitored at another center for 4 years with diagnosis of bronchiectasis. She had cough, wheezing, and sputum occasionally. She has received antibiotic treatment for tonsillitis, pharyngitis, and sinusitis many times. She was diagnosed with bronchiectasis with cough, wheezing, and failure of breath in a different hospital. Bronchiectasis had been diagnosed by chest computed tomography. The medial segment of the middle lobe of the right pulmonary lobe and the postero basal segment of the inferior lobe of the right pulmonary lobe were observed to have interstitial fibrous bands and extensive cystic bronchiectasis. She had also been operated on for eye problems. The patient was operated on for nystagmus at 2 years of age. Her grandfather and paternal aunt both had type 2 diabetes mellitus. At physical examination, she was oriented. Hyperpigmentation was present over the areola and acanthosis nigricans under the arms and on the neck (Fig 1). The patient’s height was 153 cm (25th percentile), body weight was 62 kg (90th percentile), body weight by height was 134% of standard, and BMI was 26.5. Her pulse rate and blood pressure were ~88 per minute and 100/50 mm Hg, respectively. Bilateral crepitant rales were present at respiratory system examination. At cardiovascular system examination, sinus rhythm was observed. Genital examination was evaluated as Tanner Stage 4. Audiologic examination revealed bilateral sensorineural hearing loss, and bilateral cataract was determined at ocular examination. There was no cataract at the time of the eye surgery. Cataracts were detected in our hospital. The patient failed the intelligence test because the patient’s visual and auditory function were impaired. Mental retardation was decided clinically because her can not appropriate answers with age-related mental status. Although the patient should be operated on bronchiectasis but patient’s family did not agree this operation. The patient was monitored by the department of chest diseases due to bronchiectasis. Laboratory examination results were alanine aminotransferase 20 U/L, aspartate aminotransferase 16 U/L, triglyceride 172 mg/dL, cholesterol 165 mg/dL, and low density lipoprotein 120 mg/dL; thyroid function tests were normal. During the oral glucose tolerance test, fasting glucose was 273 mg/dL, fasting insulin 35.2 mg/dL, C-peptide level 6.29 ng/mL, postprandial glucose 475 mg/dL, postprandial insulin 37.5 mg/dL, and postprandial C-peptide level 8.1 ng/mL; to evaluate insulin reserve, a significant response was obtained to the glucagon stimulation test (highest C-peptide level 9.67 ng/mL). HbA1c was 13.1%. Insulin antibodies, islet cell antibodies, and GAD65...
autoantibodies were negative. Abdominal ultrasound revealed grade 1 hepatosteatosis, increased bilateral renal dimensions, and a grade 1 rise in renal parenchyma echo. In our case, an insertion resulting in frameshift (c.2905insT) p.Leu968Leufs*4 and nonsense (c.5586T>G) p.Tyr1862* mutations were detected in ALMS1. Exon 8 of the ALMS gene was analyzed by direct sequencing with the ABI 3130 (Applied Biosystems, Foster City, CA) capillary electrophoresis system. Sequences were compared with ALMS1 (GenBank NM_015120.4; AC074008.5). The axoneme structure of nasal mucosa of the patient is seen normal in the electron microscopy. Saccharin test was positive. Our patient’s saccharin test result was 50 minutes (normal range 7–15 minutes). Alström syndrome was considered on the basis of type 2 diabetes mellitus, acanthosis nigricans, sensorineural hearing loss, and bilateral cataract and it was confirmed by genetic diagnostics. Insulin glargine 25 U/d and metformin therapy 850 mg twice daily was started. HbA1c was 8.2% after 3 months. The case is in the 12th month of observation, and blood sugar levels and cardiac and hepatic function are monitored regularly.

**DISCUSSION**

The diagnosis of Alström syndrome must be considered in children with retinal dystrophy, sensorineural hearing loss, insulin resistance and obesity, and cardiomyopathy in infancy or adolescence. Other features that may present are short stature, bladder instability, chronic renal and hepatic dysfunction, early-onset type 2 diabetes, and hypothyroidism, hypertriglyceridermia, hypogonadism, and kyphoscoliosis. Early diagnosis is important for the opportunity to introduce effective therapies for heart failure, diabetes, hyperlipidemia, and renal impairment. In research including 182 patients, dilated cardiomyopathy, type 2 diabetes mellitus, hyperinsulinemia, hypertriglyceridermia, urologic dysfunction, gastrointestinal disturbances, pulmonary symptoms, neurologic symptoms, and developmental motor or language delays were observed in 60%, 82%, 92%, 54%, 48%, 35%, 53%, 20%, and 46% of patients, respectively. Our patient had truncal obesity, acanthosis nigricans, retinal degeneration, mental retardation, sensorineural deafness, hyperinsulinism, type 2 diabetes mellitus, and hyperlipidemia. There was no cardiomyopathy, hypothyroidism, gastrointestinal disturbances, or urologic or hepatic dysfunction.

So far, 106 different disease-causing mutations have been described in the ALMS1 gene, including nonsense (55%), indels (42%), rare compound frameshift, and splice site (3%). The patient has 3 mutant alleles, which are a frameshift p.Leu968Leufs*4 mutation in a heterozygous state and a nonsense p.Tyr1862* mutation in a homozygous state. p.Leu968Leufs*4 results in frameshift in the ORF of ALMS1 and creates a termination codon after 4 amino acids and p.Tyr1862* directly leads to a truncated ALMS1 protein. Because these 2 allelic variations seem to be disease causing, we have predicted that 2 mutant alleles came from either parent in cis state and 1 mutant allele from the other parent. As DNA samples of parents were not available, we were not able to confirm the parents’ sequence. There were no clinical symptoms of Alström syndrome in other family members. It is possible that the sibling of the patient, who died at age 6 months, had infant cardiomyopathy of Alström syndrome.

Both Alström syndrome and Bardet-Biedl syndrome may have chronic respiratory symptoms and even bronchiectasis, suggesting clinical overlap with primary ciliary dyskinesia. The axoneme structure of nasal mucosa of the patient is seen normal in the electron microscopy. Saccharin clearance time is normally 7 to 15 minutes. If saccharin clearance time is longer than 20 minutes, it shows the pathology of mucociliary clearance. The saccharin test of our patient was positive. Our patient’s saccharin test result was 50 minutes. Alström syndrome is predisposed to asthma, although Alström syndrome has not been reported with bronchiectasis in the literature. Currently only 2 pharmacological options are approved for use in children with diabetes mellitus plus Alström syndrome (metformin and insulin), so we started these therapies.

**CONCLUSIONS**

We emphasize that Alström syndrome may be complicated by bronchiectasis and ciliary dysfunction.

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Pediatrics 2014;133;e780; originally published online February 17, 2014;
DOI: 10.1542/peds.2013-0284

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