Alström Syndrome With Subclinical Insulin-Resistant Diabetes and Hepatic Dysfunction: A Family Report

Ping-I Chou, MD
Chiao-Hong Chen, MD
Jiunn-Torng Chen, MD
Liang-Yen Wen, MD
Du-An Wu, MD
Steven E. Feldon, MD

INTRODUCTION

Alström syndrome is an autosomal recessive disorder characterized by obesity, sensorineural deafness, and cone-rod dystrophy appearing during the first decade of life. Detailed light and ultrastructural histopathology reveals a total absence of rods and cones, intraretinal melanin pigment, retinal pigment epithelium atrophy, and focal chorioretinal fusion. Diffuse areas of chorioretinal atrophy and large clumps of pigment develop later in the disease process.

Male patients usually display hypergonadotropic hypogonadism but are normally virilized. Chronic nephritis and diabetes caused by insulin resistance occur later, usually in the second or third decade of life. Late-appearing manifestations include hepatic failure, dilated cardiomyopathy, and renal failure.

There are many similarities between Alström syndrome and Leber’s congenital amaurosis especially in the early stages of disease when systemic findings are not apparent. Correct diagnosis may be elusive in infancy because accurate determination of vision, hearing, and mental capacity is difficult. Other findings such as diabetes mellitus and renal impairment in Alström syndrome patients usually do not develop until adolescence.

The pigmentary retinal degeneration of Alström syndrome also may be confused with Bardet-Biedl syndrome. Retinal pigmentary degeneration, hypogonadism, and obesity are present in both syndromes. Severe visual loss occurs at a younger age in patients with Alström syndrome. There is a higher incidence of neurogenic deafness and diabetes mellitus in patients with Alström syndrome, but a lower incidence of mental retardation and digital anomalies than in Bardet-Biedl syndrome. Other unusual pigmentary retinopathies that must be distinguished from Alström syndrome include renal retinal dysplasia, Laurence-Moon syndrome, and Usher’s syndrome.

The following cases in siblings emphasize the importance of serial systemic workup for subclinical diabetes and hepatic dysfunction. The early detection of systemic manifestations helps characterize the disease, thereby narrowing the differential diagnosis and facilitating early genetic counseling.

CASE REPORTS

The two cases reported are siblings who were the full-term products of two normal pregnancies. Two older siblings died soon after birth, one of sepsis and one of an unknown cause. Both parents appeared healthy with a family history positive only for diabetes mellitus in one of the paternal grandparents.

Case 1

A 12-year-old girl developed searching nystagmus, poor ocular fixation, and poor response to environmental stimuli in early childhood. Visual acuity in each eye had been no light perception.
bilaterally for the past 5 years. Posterior subcapsular cataracts were present in both eyes. Both fundi revealed waxy, pale discs with attenuated retinal vessels. There was a diffuse pepper-and-salt appearance in the posterior pole and granular depigmentation of the midperipheral retina (Figure 1). Nerve fiber bundle defects were seen in the superior temporal and inferior temporal arcades. Fluorescein angiography revealed diffuse to confluent window defects throughout the posterior and midperipheral retina (Figure 2). The electroretinogram (ERG) showed no photopic or scotopic response. The patient's secondary sexual characteristic development corresponded to Tanner stage I. Her intellectual abilities and general conditions were normal until progressive hearing loss developed. Acanthosis nigricans had recently developed in the posterior aspect of her neck.

Case 2

Poor visual acuity and searching nystagmus were first noted in infancy in the 10-year-old brother of case 1. His visual acuity was 2/200 in both eyes without color sense. The anterior segment was clear bilaterally. The fundi showed waxy, pale discs, attenuated retinal vessels, and retinal pigment degeneration (Figure 3). Nerve fiber bundle defects were evident. No ERG waveform could be detected. Psychomotor and intellectual development were normal. There was no gynecomastia and no external genital development, consistent with Tanner stage I. He was admitted at the same time as his sister due to recently developed hearing impairment and weight gain.

Laboratory Findings

Each family member underwent detailed laboratory examinations (Table 1). Plasma aspartate aminotransferase and alanine aminotransferase concentrations were elevated in both siblings. Elevated fasting plasma triglyceride, glucose and low level of high-density lipoprotein cholesterol levels in the sister were consistent with the diagnosis of diabetes mellitus complicated by dyslipidemia. The baseline levels of plasma leptin concentrations in both siblings and the father were higher than in the normal population with respect to ideal body mass index. Leptin is a plasma protein synthesized in adipose tissue. The higher baseline serum leptin levels correlated well with insulin resistance and obesity. The oral glucose tolerance test showed normal response of plasma glucose for all family members, but a remarkable elevation of corresponding insulin concentrations was noted in both siblings.
Insulin suppression testing revealed insulin resistance in the mother and both siblings.

**DISCUSSION**

The presence of retinal pigmentary degeneration causing early-onset night blindness, progressive hearing loss, obesity, noninsulin-dependent diabetes mellitus, acanthosis nigricans, hypogonadism, and the absence of polycystic or mental retardation confirmed the diagnosis of Alström syndrome in these two siblings. The sister had diabetes mellitus with extreme insulin resistance. Although diabetes mellitus was not found in any other family members, the brother had extreme insulin resistance and the mother showed mild insulin resistance. The brother is highly likely to develop diabetes mellitus.

Hepatic dysfunction is less common in Alström syndrome. Only two such cases have been reported in Asian countries. The elevated levels of liver enzymes found in these siblings may lead to hepatic cirrhosis in the future. Infantile cardiomyopathy was reported in 18 of 22 Alström syndrome patients, and 5 of those suffered cardiac deaths. Despite normal electrocardiogram findings, this risk factor should be evaluated carefully in the follow up of each of our patients. Although renal function was normal at the time of presentation, it is important to bear in mind that renal disease is a constant, but age-related feature. Twelve of the 15 reported cases had laboratory evidence of renal dysfunction, and 3 eventually died of renal failure.

The manifestation of ocular involvement in patients with Alström syndrome includes severe visual loss, searching nystagmus, posterior subcapsular cataracts, pigmentary degeneration of the retina without bone spicule formation, optic disc pallor, narrow retinal arteries, asteroid hyalosis,
and optic disc drusen (Table 2). The presence of diabetes mellitus may account for the high prevalence of posterior subcapsular cataract in Alström syndrome.

### CONCLUSION

Pigmentary degenerations of early childhood are present in a large number of inherited syndromes. In such patients, other systemic manifestations may be difficult to evaluate or may not become apparent until later in life. Therefore, the use of laboratory testing, looking specifically for subclinical hepatic, renal, and endocrine malfunction, is essential to establish a correct diagnosis early in life when effective genetic counseling can be performed and clinical expectations can be discussed with the parents.

### REFERENCES