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A Case of Alstrom Syndrome with Insulinopenia

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Abstract

A 17-year-old girl born to non-consanguinous parents presented a history of optic atrophy, Retinitis pigmentosa for eight years, followed by squint and nystagmus after two years. She developed progressive bilateral sensory neural hearing loss at the age of 12. She had menarche spontaneously at 14 years, but her cycles have been irregular ever since. She was diagnosed with dilated cardiomyopathy at 16 years, followed by Type 2 diabetes at 17 yrs. Hence the clinical diagnosis of Alstrom syndrome (AS) was made based on clinical criteria. She also developed renal impairment and needed frequent hospital admissions with congestive heart failure. She died at the age of 21 years due to cardiac failure. Interestingly she was not obese and insulin-resistant as reported earlier but lean and insulinopenic. The rarity and insulinopenia, an unusual aspect of the case, deserved to be published.

Keywords: Case report, Astrom, Diabetes, Optic Atrophy, Deafness

Introduction

Alstrom syndrome is a sporadic autosomal recessive disease. Alstrom et al. described the clinical features of three patients in a paper published in 1959,[1]in which they give a detailed phenotype of these patients, showing a combination, inherited and recessive, of retinal degeneration, obesity, neurosensorial deafness, and type 2 diabetes mellitus (T2DM). The estimated prevalence for Alstrom (ALMS) is one to nine cases per 1,000,000 individuals[2] with nearly 700 cases described worldwide to date. Symptoms appear in childhood with great variability in clinical evolution and severity. This variability has been described among patients with identical mutations within the same family. Marshall et al. reported an in-depth revision of the ALMS clinical phenotype. However, some atypical, extreme cases with mutations in the *ALMS1* gene[2] have been described ever since, either without nystagmus, photophobia, obesity, and hearing loss or only with mitogenic cardiomyopathy. *ALMS1* gene is linked to Alstrom and located on chromosome 2p13. It consists of 23 exons predicted to encode a large protein of 4,169 amino acids, and its biological role is still being elucidated. Life expectancy is less than 50 years, and they die of cardiac or renal failure. Early diagnosis of ALMS is complicated by the progressive onset of the associated symptoms and its own inter and intrafamilial clinical heterogeneity.

Narrative

17 yrs old girl had Visual deterioration since the age of 8 years, and Ophthalmologist noted, Optic atrophy and Retinitis Pigmentosa. It was followed by Nystagmus and squint after two years. No other neurological signs were noted then. She dropped school studies because of visual difficulties. Later her hearing started to impair from the age of 12. The audiological evaluation showed the sensory neural type of hearing loss. She attained menarche spontaneously at 14 years of age, and her menstrual cycles have been irregular ever since. She developed breathlessness, pedal edema, and ascites at the age of 16. Clinically she had evidence of congestive heart failure, and an echocardiogram showed dilated cardiomyopathy. She was started treatment for heart failure. Then She developed scoliosis, but no vertebral or disc or neurological diseases were found. At 17 years, she was investigated for polyuria, and Laboratory investigations showed Fasting blood sugar of 187mgm%, HbA1c- 8.6%, low C- peptide (0.3 mcg/dl), negative Anti Glutamic acid decarboxylase 65 (GAD65)

antibody, but her triglycerides were elevated (360mg%). Hence Type 2 Diabetes Mellitus was diagnosed and put on insulin therapy. Diagnosis of Alstrom's syndrome was arrived at using clinical criteria.

But interestingly, she was lean with a BMI of 21 and had no signs of insulin resistance like acanthosis nigricans as most of the reported cases of Alstrom were obese with signs of insulin resistance [8,9]. She was treated with metformin, insulin, and heart failure medications. She needed frequent hospital admissions for the management of cardiac failure. Her renal functions also deteriorated at the age of 18 years, and no primary renal causes were found. She died at the age of 21 due to cardiac failure. Genetic testing was not done because of a lack of affordability.

Table 1

Age (years)	Major Criteria	Minor Criteria	Other supportive evidence	Diagnosis
≤ 2*	• *ALMS* 1 mutation in 1 allele and/or family history of AS • Vision (nystagmus, photophobia)	• Obesity • DCM/CHF	• Recurrent pulmonary infections • Normal digits • Delayed developmental milestones	2 major criteria OR 1 major + 2 minor criteria
3–14	• *ALMS* 1 mutation in 1 allele and/or family history of AS • Vision (nystagmus, photophobia, decreased acuity, cone dystrophy by ERG**)	• Obesity and/or insulin resistance • (History of) DCM/CHF • Hearing loss • Advanced bone age • Hepatic dysfunction • Renal failure	• Recurrent pulmonary infections • Normal digits • Delayed developmental milestones • Hyperlipidemia • Scoliosis • Flat wide feet • Hypothyroidism • Hypertension • GH deficiency • Recurrent UTI	2 major criteria OR 1 major + 3 minor criteria
≥ 15	• *ALMS* 1 mutation in 1 allele and/or family history of AS • Vision (legal blindness, history of nystagmus in infancy/childhood, cone and rod dystrophy by ERG)	• Obesity and/or insulin resistance and/or DM2 • (History of) DCM/CHF • Hearing loss • Hepatic dysfunction • Renal failure • Short stature • Males – hypogonadism • Females – irregular menses and/or hyperandrogenism	• Recurrent pulmonary infections • Normal digits • History of developmental delay • Hyperlipidemia • Scoliosis • Flat wide feet • Hypothyroidism • Hypertension • GH deficiency • Alopecia • Recurrent UTI or urinary dysfunction	2 major + 2 minor criteria OR 1 major + 4 minor criteria

Discussion

Alstrom syndrome (AS) was first described in 1959 and had an estimated prevalence of<1:100 000 [1]. AS is an autosomal recessive multi-organ disorder characterized by childhood obesity [1,8], adult short stature with initial accelerated childhood linear growth, progressive cone-rod dystrophy leading to blindness, and sensorineural hearing loss [3,4]. Endocrinologic complications include early-onset diabetes mellitus (typically in the 2 or 3decades)[6,9], hyperinsulinemia (with associated acanthosis nigricans), hypertriglyceridemia[5], infertility (hyper gonadotrophic hypogonadism)[11], and hypothyroidism [4-6]. Systemic fibrosis is commonly observed [3]. The primary cause of mortality among young affected patients is cardiac involvement from dilated cardiomyopathy, whereas renal failure[10] is the major cause of death among the older subgroup [2,3]. Mutations in the *ALMS1* gene were independently identified as causative for AS by two research groups. *ALMS1* encodes a protein of 4169 amino acids, which includes a large tandem-repeat domain consisting of 47 amino acids (aa)[7]; the exact function of the ALMS1 protein remains unknown. Several mutations have been described

in this gene, being exons 8, 10, and 16 hotspots for *ALMS1* mutations (variations in exon eight accounts for 49% of the total mutation load in ALMS). More than 200 mutations have been reported. Next-generation sequencing, like whole-exome sequencing (WES) and whole-genome sequencing, has revolutionized the approach to finding novel mutations to account for phenotypic variability and predicting prognosis.

Before the recent discovery of *ALMS1* mutations causative for AS, the diagnosis of AS was made solely based on phenotype. However, AS exhibits a great degree of phenotypic variability, even within families, thereby creating difficulties for a universal definition of AS. Marshall et al. defined AS using age-specific criteria [3]. (Table 1)

It remains important to distinguish AS from other disorders characterized by childhood obesity and retinal dystrophy, such as the Laurence-Moon and Bardet-Biedl syndromes. Normal mentation and lack of poly/syndactyly help distinguish AS from Bardet-Biedl, while deafness and the absence of spastic paraparesis help differentiate AS from Laurence- Moon. Refsum disease is a rare disorder characterized by hearing loss, visual loss, and hepatic involvement but also includes several features not associated with AS.

Our case had most of the described features of AS like optic atrophy, nystagmus, squint, sensory neural hearing loss, Scoliosis, Type2 diabetes, hypertriglyceridemia, dilated cardiomyopathy, and renal impairment. But she lacked features like obesity and insulin resistance like acanthosis nigricans and hyperinsulinemia. On the contrary, she was lean and insulinopenic, needing insulin therapy for diabetes. The reason for reporting this case is the rarity and variation in phenotype.

Conclusion

Alstrom syndrome case is a rare disease with varied phenotypes. With retinal degeneration, obesity, neurosensorial deafness, dilated cardiomyopathy and type 2 diabetes mellitus being central theme. Our case has most of the features but interestingly not obese and insulinopenic which prompted us to publish the case.

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