Alström syndrome: A rare association of retinitis pigmentosa with insulin resistance syndrome

Sir,

Alström syndrome (AS) is an autosomal recessive, single-gene disorder with multisystem involvement. The life span of patients with AS rarely exceeds 40 years. There is no specific therapy for AS. As it is autosomal recessive, the birth of an affected child establishes each parent as a heterozygous carrier. Carriers of mutations in *ALMS1* do not show any signs of the disease. In most cases, there is no previous family history of the condition.

We evaluated a 15-year-old girl for secondary amenorrhea and excessive hair growth on the face. On examination, she was found to have alopecia, hirsutism, acanthosis, and large sweaty hands. Investigations revealed transaminitis (sixfold high enzymes), high blood sugars, and high serum triglyceride level. Type 2 Diabetes Mellitus (T2DM) was diagnosed on the basis of oral glucose tolerance test (OGTT). Hormonal profile of the patient revealed high testosterone levels with normal follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, thyroid stimulating hormone (TSH), and growth hormone levels. USG showed features of polycystic ovarian syndrome. Magnetic resonance imaging (MRI) brain was normal. One year later, the patient complained of diminution of vision and photophobia. Visual acuity was 6/18. Perimetry showed bilateral constriction of visual field. Fundus examination revealed waxy disc pallor, arteriolar attenuation, and bony spicule pigmentation [Figures 1 and 2]. On the basis of the above findings and electroretinogram ERG, a diagnosis of retinitis pigmentosa (RP) was made. Pure tone audiometry PTA of the patient was normal. AS was suspected in view of T2DM, hepatic dysfunction (transaminitis), hyperandrogenemia, hypertriglyceridemia, and RP. A definitive diagnosis would have been possible by doing chromosomal mutational analysis which could not be done due to financial constraints.

AS is a rare genetic disorder caused by mutations in the gene *ALMS1*, a novel gene of currently unknown molecular function. It was first described by Carl-Henry Alström in Sweden in 1959.[1] The key features are childhood

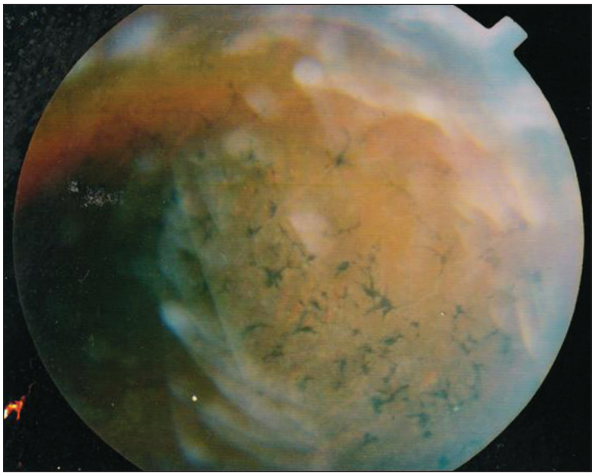

Figure 1: Bony spicule retinal pigmentary changes

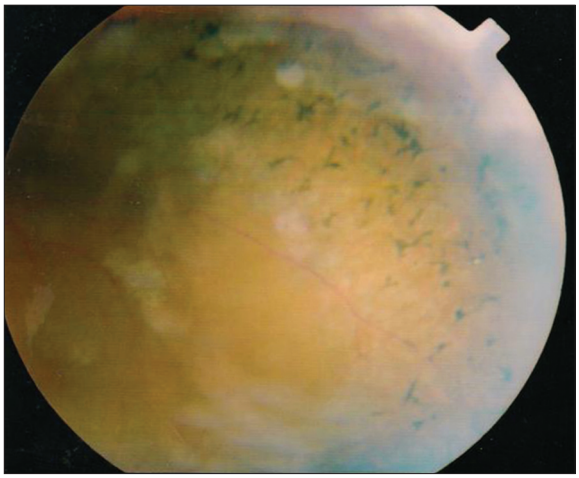

Figure 2: Retinal pigmentary changes in retinitis pigmentosa

obesity, blindness due to congenital retinal dystrophy, and sensorineural hearing loss. Associated endocrinologic features include hyperinsulinemia, early-onset Type 2 Diabetes, and hypertriglyceridemia. Thus, AS shares several features with the common metabolic syndrome, namely obesity, hyperinsulinemia, and hypertriglyceridemia. Mutations in the *ALMS1* gene have been found to be causative for AS, with a total of 79 disease-causing mutations having been described.[2]

Diagnosis of AS can be difficult because some features begin at birth and others emerge as the child develops. Marshall *et al.* have provided a comprehensive guidance for diagnostic criteria in their 2007 publication.[3] For children above 15 years, the diagnosis requires two major and two minor criteria or one major and four minor criteria. The major criteria are: 1) *ALMS1* mutation in one allele and/or family history of AS and 2) vision pathology (history of nystagmus in infancy/childhood, legal blindness, cone and rod dystrophy by ERG). The minor criteria are: 1) obesity and/or insulin resistance and/or Type 2 Diabetes; 2) history of dilated cardiomyopathy with congestive heart failure; 3) hearing loss; 4) hepatic dysfunction; 5) renal failure; 6) short stature; and 7) males: Hypogonadism, females: Irregular menses and/or hyperandrogenism. Other supportive features include recurrent pulmonary infections, normal digits, history of developmental delay, hyperlipidemia, scoliosis, flat wide feet, hypothyroidism, hypertension, recurrent urinary tract infections/urinary dysfunction, growth hormone deficiency, and alopecia.

The similarity to other syndromes and delay in onset of some of the clinical features often results in misdiagnosis.[4] Clinical features such as the early age of onset of cone dystrophy, hearing loss, and obesity in childhood, dilated cardiomyopathy (DCM), T2DM, normal intelligence (but delay of developmental milestones), absence of digital anomalies, and advanced bone age with reduced final adult height can be helpful in distinguishing this syndrome from closely related disorders.[5]

There is, thus far, no treatment that can cure AS or prevent or reverse the medical complications. Children with AS require a detailed history and thorough initial assessment, along with intensive medical management and multidisciplinary follow-up to anticipate and detect the complications that can be treated. Careful monitoring of the systemic manifestations and prompt intervention can generally improve the overall outcome.

Irfan Yousuf Wani, Ashraf Ganie[1], Iqra Mehraj[2], Yasser Yousuf Wani[2], Muzafar Naik

Department of Internal Medicine, SKIMS MCH, Bemina, Srinagar, [1]Department of Endocrinology, SKIMS, Srinagar, [2]Department of Health Services, Kashmir, J and K, India

Corresponding Author: Dr. Irfan Yousuf Wani, House No 100, Lane No 9. Kanitar, Srinagar, Kashmir - 190 006, India. E-mail: drirfanyousuf@gmail.com

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