

## SEVERE INSULIN RESISTANCE AND RECURRENT PANCREATITIS IN AN 18-YEAR-OLD WITH ALSTRÖM SYNDROME

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### ABSTRACT

Alström syndrome is a rare autosomal recessive disorder caused by mutations in *ALMS1*. Insulin resistance is one of the earliest metabolic changes in Alström syndrome and progresses in severity more rapidly than that seen in the general population. We describe an 18-year-old female with Alström syndrome who presented with obesity, severe insulin resistance, and recurrent pancreatitis at a very early age. Despite good compliance and intense insulin therapy, her glycemic control remains inadequate. The expression of the *ALMS1* protein in the hypothalamus may contribute to hyperphagia, resulting in obesity. A better understanding of the factors that contribute to severe insulin resistance may help improve glycemic control and offer more effective treatment in this multisystem disease.

### INTRODUCTION

Alström syndrome (AS) (OMIM #203800) is a rare autosomal recessive (AR) disorder first described in 1959.<sup>1</sup> Worldwide, there are approximately 800 known cases since its discovery.<sup>2</sup> The disorder is caused by mutations in *ALMS1*, located on chromosome 2p13. The *ALMS1* protein is ubiquitous and localizes to centrosomes and basal bodies in primary cilia of cells. It is thought to have roles in primary ciliary function, cell cycle control, and intracellular transport in multiple organ systems.<sup>3-5</sup> Multi-organ pathologies begin during infancy and usually shorten life expectancy. Clinical features include blindness, deafness, obesity, hypogonadism, and cardiomyopathy.<sup>5</sup> We describe an 18-year-old female with AS who developed severe insulin resistance (IR) and recurrent pancreatitis.

### CASE REPORT

Shortly after birth, a previously healthy female presented with nystagmus and low vision secondary to a cone-rod dystrophy, ultimately leading to complete blindness. By age 6, sensorineural hearing impairment was noted along with obesity, glucose intolerance, and hypertension. Her clinical presentation suggested AS, and genetic analysis confirmed compound heterozygous mutations in exons 8 and 16: c.6305C>A; p.Ser2102\* and c.10775delC; p.Thr3592Lysfs\*6) of *ALMS1*.

Shortly after the diagnosis of AS at age 6, an oral glucose tolerance test (OGTT) was performed and showed a 2-

hour blood glucose level of 297 mg/dL, consistent with the diagnosis of type 2 diabetes mellitus (T2D). She was initially treated with metformin monotherapy; insulin was added 2 years later. Despite good compliance and aggressive daily basal-bolus insulin, her glycemic control remained inadequate. To facilitate insulin delivery, she was switched to continuous subcutaneous insulin infusion (CSII) using U-500 insulin. Insulin requirements often exceed 300 units a day.

At 18 years old, her intellectual function was normal. Physical examination revealed abdominal obesity (BMI 26.7 kg/m<sup>2</sup>), prominent acanthosis nigricans, and hirsutism. She underwent menarche at 12 years of age, but subsequently experienced secondary amenorrhea.

Poor glycemic control and hypertriglyceridemia often coexist<sup>6</sup> but appear to have no clear correlation in our patient (**Figure 1**). Dietary fat and carbohydrates were restricted and daily exercise encouraged. With combined dietary and medical management (fenofibrate, omega-3 fatty acid, metformin and insulin), since age 13 a sustainable reduction in her hypertriglyceridemia has been noted (**Table 1**).

Within the past 5 years, she has experienced 13 episodes of acute pancreatitis requiring hospitalization. During treatment for pancreatitis, she was able to maintain adequate glycemic control while receiving dextrose-containing IV fluids. However, when oral feedings were resumed, marked postprandial hyperglycemia occurred,

Figure 1. HbA1c and Triglyceride Levels

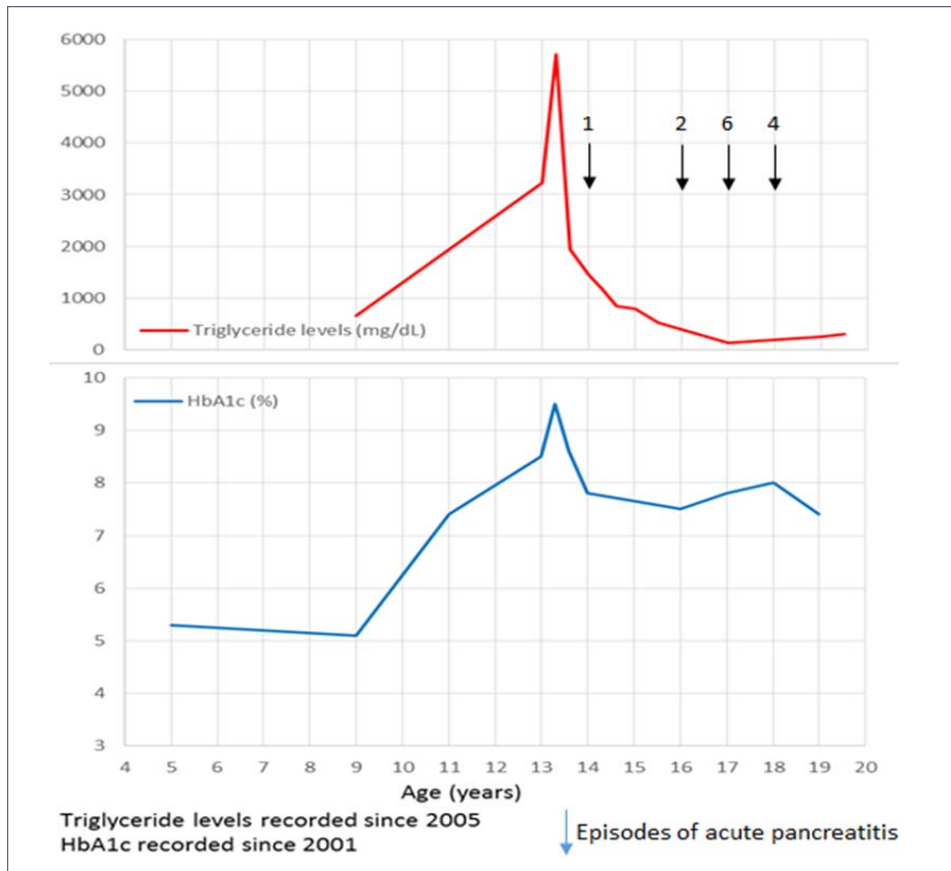


Table 1. Changes in Lipids and Lipoproteins (mg/dL) with Treatment. †

Date (Age in years)	TC	TG	HDL-C
Aug-05 (9)	166	658	24
May-09 (13)	310	3230	12
Jul-09 (13)	410	5710	9
Sep-09 (13)	290	1940	18
Jan-10 (13)	284	1462	19
Jul-10 (14)	313	1160	23
Sep-10 (14)	267	849	19
Mar-11 (15)	255	801	19
Sep-11 (15)	237	521	25
Feb-13 (16)	285	135	17
Goal*	< 170 mg/dL	< 150 mg/dL	> 50 mg/dL

\*Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. Pediatrics. 2011;128:S213-S256.

†Treatment includes fenofibrate, omega-3, metformin and insulin.

despite significant amounts of pre-prandial rapid acting insulin analog. Restriction of carbohydrate intake allowed reduction in her insulin dosages and improved glycemic control. Compliance with a low fat and carbohydrate restricted diet has been challenging.

## DISCUSSION

The ALMS1 protein localizes to centrosomes at the base of the primary cilia and is ubiquitously expressed in nearly all tissues.<sup>7</sup> Fibroblasts that express the dysfunctional ALMS1 protein are able to synthesize normal appearing primary cilia, suggesting mutations in ALMS1 lead to abnormal function rather than structure. Deficits in primary ciliary function help explain the characteristic multi-system involvement of AS.<sup>8</sup> Primary cilia, located at the cell surface of most eukaryotic cells, serve important roles in chemosensation, mechanosensation, and intra- and extra-cellular signal transmission.<sup>9</sup> Although there is extensive allelic heterogeneity, the varying severity of symptoms often seen within the AS population suggests that additional environmental or other genetic factors modulate the clinical expression of the disorder.<sup>7</sup>

IR and hyperinsulinemia are two of the earliest metabolic changes seen in individuals with AS.<sup>10</sup> T2D is present in nearly 70% of those over the age of 16, but has been documented as early as 2-4 years of age.<sup>2</sup> IR in AS is usually associated with obesity and hyperphagia.<sup>7</sup> Newborns with AS are of normal birth weight but exhibit rapid weight gain and truncal obesity during the first or second years of life.<sup>7</sup> Hyperphagia is common and may be caused, in part, from expression of the ALMS1 protein in the hypothalamus.<sup>7</sup> The early onset of obesity along with the presence of ALMS1 in other organs such as the pancreas and liver, may explain the accelerated development and increased severity of IR seen in Alström syndrome.<sup>7</sup>

Although glycemic control may be achieved with large doses of insulin, carbohydrate restriction appears to be the key factor in avoiding hyperglycemia in our patient. Furthermore, carbohydrate restriction has been shown to be more effective than fat restriction in preventing hyperglycemic episodes in other cases of AS as well.<sup>11</sup> Blood glucose levels and basal insulin levels increased several-fold after a high-carbohydrate meal, but not after a high-fat or low-carbohydrate meal.<sup>11</sup> Thus, when carbohydrate intake is carefully controlled, adequate glycemic control may be achievable.

Disruption of ALMS1 in mouse models have shown to reduce insulin-stimulated GLUT4 trafficking to cell membranes.<sup>12</sup> In addition to dietary modifications, increased aerobic physical activity may be beneficial in reducing hyperglycemia by facilitating GLUT4 receptor mobilization.<sup>11,13</sup> One case report has demonstrated that increased aerobic activity can lead to remission of T2D in AS.<sup>13</sup>

The increased incidence of acute pancreatitis in the AS population seems to be closely associated with both severe hypertriglyceridemia and insulin resistance. Paisey *et al.* found that 100% of AS patients with severe hypertriglyceridemia (> 8 mmol/L) developed pancreatitis. Of those with pancreatitis, all had T2D, severe IR, and hyperinsulinism.<sup>6</sup> Clearance of triglycerides from the plasma may be reduced due to the inability of insulin to activate lipoprotein lipase. Furthermore, reduced translocation of GLUT4 receptors on adipocytes and cardiomyocytes may shuttle excess circulating glucose to hepatocytes via GLUT2 receptors, providing excess substrate for hepatic triglyceride production.<sup>14</sup>

## CONCLUSION

AS is a rare, multisystem disorder, caused by mutations in ALMS1, leading to primary ciliary dysfunction. Key features include hearing loss, visual impairment, obesity and severe IR. The exact mechanism(s) by which primary ciliary dysfunction leads to the multiple clinical manifestations is unknown. T2D seen in AS manifests early and rapidly progresses to hyperinsulinemia and severe IR. In addition to standard diabetes therapy, adequate glycemic control requires limitation of carbohydrate intake, increased aerobic physical activity, and weight control. Triglyceride lowering medications and supplements may also be beneficial. Although ALMS1 may not play a major role in the general population affected by T2D and pancreatitis, a better understanding of the gene mutation may lead to more effective management of these diseases.

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