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Case Report

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Inappropriate treatment of diabetes in an adult patient with alström syndrome: effect of adding metformin

Abstract

Alström syndrome (ALMS) is a rare autosomal recessive condition characterized by childhood onset cone-rod retinal dystrophy leading to juvenile blindness, neuronal hearing loss, obesity, insulin resistance (IR) and type 2 diabetes mellitus. Although the mean age of onset for diabetes is 15, diabetes can be diagnosed in these patients as early as age 5years. Younger patients rarely need insulin, but some patients require insulin in very high doses long term. Many respond to the treatment with insulin-sensitizing agents such as metformin or thiazolidinediones (TZDs). A 22-year-old man with Alström syndrome, who does not respond well to insulin treatment, was admitted to our clinic. He was on regular insulin (330u/day). At admission, his fasting blood glucose (FPG) was 169mg/dL, HbA1c was 8.7%, fasting serum insulin was 88mIU/mL, c-peptide was 3.77ng/mL. He was started on Metformin 2550mg/day additional to the insulin regimen. Because of hypoglycemic episodes, insulin doses were gradually decreased and then stopped in one month. Treatment was continued only with metformin. 3months later, his FPG was 141mg/dL, and HbA1c was 7.7%. Insulin resistance with hyperinsulinemia and progression to type 2 diabetes mellitus are common in patients with Alström syndrome, and in this case, metformin proved effective and allowed cessation of insulin therapy.

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Abbreviations: FPG, fasting plasma glucose; TSH, thyroid stimulating hormone; FT4, free T4; AST, aspartate transaminase; ALT, alanine Aminotransferase; WBC, white blood cell count; ALMS, alström syndrome; IR, insulin resistance

Introduction

Alström syndrome (ALMS) is a rare autosomal recessive condition characterized by childhood onset cone-rod retinal dystrophy leading to juvenile blindness, neuronal hearing loss, obesity, insulin resistance (IR) (with associated acanthosis nigricans) and type 2 diabetes mellitus.[1] Mutations in ALMS1, a large gene on chromosome 2p13, causes ALMS.[2] Very high incidences of comorbid disease phenotypes including endocrine abnormalities, dilated cardiomyopathy, pulmonary fibrosis and restrictive lung disease, and progressive hepatic and renal failure may severely affect prognosis and survival. Hypertension, hypothyroidism, mixed hyperlipidemia (predominantly hypertriglyceridemia), primary hypogonadism in males and hyperandrogenism in females, growth hormone deficiency, urological abnormalities, adult short stature, and bone-skeletal disturbances are other clinical features seen in some patients.[3–5] Most patients have normal intelligence, although some reports indicate delayed psychomotor and intellectual development.[3] Systemic fibrosis is commonly observed.[4] Diagnosis of Alström Syndrome can be challenging because some features begin at birth and others appear as the child develops.[3] Coronary artery disease and pneumonia can cause premature death in adults whereas renal involvement are the leading cause of death among the older subgroup.[4,6,7]

Management of IR and diabetes mellitus in patients with Alström Syndrome includes weight reduction and physical exercise although vision loss can make some kinds of exercise difficult.[8] There is variable responsiveness of treatment to hyperglycemia. Younger patients rarely need insulin, but some patients require very high doses of insulin in the long term. Many respond to the treatment with insulin-sensitizing agents such as metformin or thiazolidinediones (TZDs). However, this necessitates close monitoring of liver, cardiac, and renal function.[3]

Here we will discuss the effect of adding metformin to the treatment regimen in a 22-year-old man with Alström syndrome whose glycemic control is poor on insulin.

Case report

A 22-year-old man with Alström syndrome, who do not respond well to insulin treatment, was admitted to our clinic. He was started on insulin therapy upon diagnosis of type 1 diabetes mellitus in mind after he has admitted to hospital with foot wound and fasting plasma glucose (FPG) of 277mg/dL while he was 13years old. Because of the high level of blood sugar, his insulin doses were increased gradually. At admission, the patient had confirmed neuronal deafness and visual impairments, gonadal dysfunction, hyperlipidemia, hypothyroidism and essential hypertension. His mother has type 2 diabetes mellitus (DM). His height was 172cm, his weight was 85 kg, and his body mass index was 28.7kg/m^2. Vital signs were normal. He had acanthosis nigricans, reduction in beard growth and small testes on physical examination. He was on regular insulin (330u/day), atorvastatin 20mg/day, carvedilol 12.5mg/day, levothyroxine 25µcg/day, testosterone injection every 4weeks. At admission, his FPG was 169mg/dL, HbA1c was 8.7%, insulin was 88mIU/mL, c-peptide was 3.77 and HOMA-IR was 32.5; other test results are shown in Table 1. He was started on Metformin 2550mg/day additional to insulin regimen. Because of hypoglycemic episodes, insulin doses was gradually decreased and then stopped in one month. Treatment was continued only with metformin. 3months later, his FPG was 141mg/dL; HbA1c was 7.7%; other test results are shown in Table 1.

Table 1 Laboratory values of the patient

	Before Metformin	After Metformin
FPG (mg/dL)	169	141
HbA1c (%)	8.7	7.7
Triglyceride (mg/dL)	172	127
Total Cholesterol (mg/dL)	232	114
LDL-Cholesterol (mg/dL)	164	60
Creatinine (mg/dL)	1.1	1.07
TSH (0,27-4,2μIU/mL)	4.28	5.57
FT4 (0,93-1,7ng/dL)	1.23	1.61
ALT (0-55U/L)	45	60
AST (5-34U/L)	27	29
ALP (30-120U/L)	-	90
GGT (0–38U/L U/L)	-	110
WBC (4000-1000)	6400	5900
Na (136-146mmol/L)	141	140
K (3.5-5.1mEq/L)	4.3	4.7
Prolactin (1.9-25ng/ml)	-	11.3
FSH (2.8-11.3 m IU/ml)	-	15.13
LH (1.9- 11.6 m IU/ml)	-	9.91
Total testosteron (240-950ng/dL)	-	749.2

FPG, fasting plasma glucose; TSH, thyroid stimulating hormone; FT4, free T4; AST, aspartate transaminase; ALT, alanine aminotransferase; WBC, white blood cell count

Discussion

Severe IR and progression to DM are common features of Alström syndrome. In one series, 92% of individuals with Alström syndrome had hyperinsulinemia in early childhood (18months-4 years). Although the mean age of onset for diabetes is 15, diabetes can be diagnosed in these patients as early as age 5years. Approximately 82% of patients over the age of 16 are diabetic.[4] Our patient was 13years old when diagnosed with diabetes mellitus.

Although the mechanisms underlying the development of hyperinsulinemia and type 2 diabetes mellitus are still unknown in ALMS; the ALMS protein is present in the centromere, suggesting an unexpectedly crucial role in the basal body and centrosome impairment in the etiopathogenesis of obesity, insulin resistance, and type 2 diabetes.[9] Bettini et al.,[10] reported that both insulin resistance and β-cell failure are the two distinguishing factors responsible for the development of glucose metabolism alterations in Alström patients. In ALMS the progression from the early onset obesity towards the impaired fasting glucose or impaired glucose tolerance and overt diabetes is mostly due to a progressive failure of β-cell insulin secretion without any further worsening of insulin resistance with age.[10] Marshall et al.,[3,4] demonstrated interstitial fibrosis present in approximately 80% of patients with Alsröm syndrome.[4]

Our patient has poorly controlled diabetes with insulin treatment. Because severe IR is a common feature of patients with Alström syndrome, metformin was added to the treatment regimen of our patient. Although insulin therapy was discontinued one month later, metformin treatment resulted in improvements in FPG and HbA1c levels. This supports the thesis of many patients with Alström syndrome responds to insulin-sensitizing agents. Thus, complications that have been associated with the use of high doses of insulin including weight gain, hypoglycemia risk, edema, allergic reactions, lipodystrophy, injection induced bleeding and pain, lipohypertrophy were eliminated. In a series of patients with Alstrom syndrome,[11] glycemic control of a patient worsened despite escalating doses of insulin. Upon switching to metformin, and resolution of the intercurrent illness, control gradually improved which is consistent with our patient's results. In a case report adding metformin at the stage of insulin resistance did not stop progression to diabetes mellitus, however, the authors propounded that combination of metformin treatment with rosiglitazone can be worthwhile in control of IR and DM in children with AS.[12]

In conclusion, insulin resistance with hyperinsulinemia and progression to type 2 diabetes mellitus are common in patients with Alström syndrome, and metformin can be effective in overcoming this. Furthermore, escalating doses of insulin may not be useful to achieve good glycemic control in all patients with severe hyperglycemia under insulin therapy.

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None.

Conflict of interest

The author declares no conflict of interest.

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