Anti-Insulin Antibody Syndrome Following Alpha-Lipoic Acid Use in Turkish Patients: Report of Three New Cases

Türk Hastalarda Alfa Lipoik Asit Kullanımına Sekonder Antiinsülin Antikor Sendromu: Üç Yeni Vaka

Abstract

Anti-insulin antibody syndrome is a rare autoimmune disorder that is characterized by severe hypoglycemia, elevated blood insulin level, insulin autoantibodies, and the absence of pancreas islet cell pathology or exogenous insulin exposure. Alpha-lipoic acid is a sulfhydryl-containing compound that is used to treat diabetic peripheral neuropathy and was first reported as a cause of anti-insulin antibody syndrome in Japan in 2003. In the literature, 17 cases with anti-insulin antibody syndrome following alpha-lipoic acid use have been reported from Japan, along with one case from Turkey, two from Korea, and seven cases from Italy. In this article, we present three cases with anti-insulin antibody syndrome developed after alpha-lipoic acid use. Case 1: A 72-year-old male patient was observed to have lost consciousness at home. This patient had no history of diabetes mellitus, diabetic medication, or insulin use. The patient complained of tiredness, palpitations, and sweating that began 3-4 hours after eating but regressed after eating during the past month. The patient had a history of diagnosis with lumbar disk hernia two months ago and was using alpha-lipoic acid (600 mg). Case 2: A 67-year-old female patient had a history of diagnosis with lumbar disk hernia two months after eating but regressed after eating during the past month. The patient had diabetes mellitus, diabetic medication, or insulin use. The patient complained of tiredness, palpitations, and sweating two to three hours after a meal that started after starting alpha-lipoic acid therapy. Case 3: A 46-year-old male patient using alpha-lipoic acid (600 mg) following the diagnosis of diabetic peripheral neuropathy. She complained of shivering and sweating two to three hours after a meal that started after starting alpha-lipoic acid therapy. Case 3: A 46-year-old male patient complained of tiredness, palpitations, and sweating for the last three weeks. Seven weeks ago, he started using alpha-lipoic acid (600 mg) after being diagnosed with carpal tunnel syndrome. The patients were diagnosed with anti-insulin antibody syndrome secondary to alpha-lipoic acid use, following which their alpha-lipoic acid therapy was discontinued. Alpha-lipoic acid is widely used in the treatment of diabetic peripheral neuropathy, nutritional support, or as an anti-aging agent. However, it should be noted that its use may cause anti-insulin antibody syndrome in genetically predisposed people.

Keywords: Hypoglycemia; insulin autoantibody; alpha-lipoic acid

Anahtar kelimeler: Hipoglisemi; insülin otoantikoru; alfa-lipoik asit

Address for Correspondence: Emine KARTAL BAYKAN, Clinic of Endocrinology and Metabolism Diseases, Erzurum Regional Training and Research Hospital, Erzurum, TURKEY

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Introduction
Anti-insulin antibody syndrome (AIAS) is a rare autoimmune disorder that was first described by Hirata in 1970. AIAS is characterized by the presence of severe hypoglycemia, elevated blood insulin levels, insulin autoantibodies, and the absence of pancreas islet cell pathology or exogenous insulin exposure (1). Most AIAS cases have been reported from East Asian countries such as Korea and Japan (380 cases between 1970 and 2009). There is limited information regarding the incidence of AIAS in regions other than Asia, with only 70 cases having been reported from Eastern Europe and the USA and 12 from Italy (2). Alpha-lipoic acid (ALA) is a sulfhydryl-containing compound that is used to treat diabetic peripheral neuropathy and was first reported as a cause of AIAS in Japan in 2003 (3). In the literature, 17 cases with AIAS secondary to ALA use have been reported from Japan, whereas only one from Turkey, two from Korea, and seven from Italy have been reported (4-6). Here, we present three cases with AIAS developed following ALA use.

Case Reports
Case 1
A 72-year-old male patient was reported to have fainted at home. When he presented to the emergency department, his blood glucose was 35 mg/dL, and dextrose was administered by vein infusion. He had no history of diabetes mellitus and the use of anti-diabetic drugs or insulin. He complained of fatigue, palpitations, and sweating that started 3-4 h after a meal but receded after food ingestion for over a month. The patient had been previously diagnosed with a lumbar disk hernia two months ago and was using ALA (600 mg). The height, weight, and body mass index (BMI) of the patient were recorded as 75 kg, 172 cm, and 25.3 kg/m², respectively. The physical examination indicated no abnormal findings or acanthosis nigricans. Based on the biochemical analysis, the glucose level was 35 mg/dL, insulin was 5470 µIU/mL (3-17), and C-peptide was >20 ng/mL (0.9-7.1); and HbA1c: 6.1%. A 75 g oral glucose tolerance test was performed. At 0 min, the levels of blood sugar, insulin, and C-peptide were 55 mg/dL, 4968 µIU/mL, and >20 ng/mL, respectively, whereas, at 60 min, these parameters were 170 mg/dL, 6754 µIU/mL, and >20 ng/mL, respectively. Hepatic, renal, and thyroid functions, pituitary hormones, complete blood count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were all normal. Protein electrophoresis was normal and serological tests for autoimmune disorders and vasculitis were negative. After one hour in the prolonged fasting test, the patient developed sweating and chills. When the blood glucose was 28 mg/dL, insulin was 5970 µIU/mL (3-17), and C-peptide was >20 ng/mL (0.9-7.1). No pancreatic abnormality was observed by abdominal computer tomography (CT) scan, abdominal magnetic resonance imaging (MR) imaging, endoscopic sonography, or Gallium 68 Positron Emission Tomography (PET) scan. The level of anti-insulin antibodies (AIA) was 370 U/mL (<0.4) (Table 1). Human Leucocyte Antigen (HLA) typing was DRB1 04:03. Based on these findings, the patient was diagnosed with AIAS, and ALA therapy was discontinued. The patient was given acarbose (50 mg, 3×1), and a diet containing complex carbohydrates was recommended. Since hypoglycemia can continue during follow-up, 1 mg/kg of pred-

| Table 1. Biochemical analysis of Case-1. |
|----------------------------------------|
| ALA treatment  | ALA stopped, Prednisolone started at 1 month | Prednisolone started at 3 months | Prednisolone started at 6 months |
|----------------|-----------------------------------------------|----------------------------------|----------------------------------|
| Glucose (70-100 mg/dL)                | 35                                            | 75                               | 81                               | 87                               |
| Insulin (3-17 µIU/mL)                 | 5470                                          | 1470                             | 460                              | 16                               |
| Anti-insulin antibody (<0.4 U/mL).    | 370                                           | 82                               | 24                               | 2                                |

ALA: Alpha-lipoic acid.
nisolone treatment was started. However, hypoglycemia was not observed during follow-up, and the patient was discharged with a recommendation of polyclinic control. During the control visit in the first month, the patient had no complaints of hypoglycemia, and the level of blood sugar was 75 mg/dL, insulin was 1470 µIU/mL, and anti-insulin antibody was 82 U/mL. Hence, the prednisolone dose was reduced to 0.5 mg/kg. During the control visit in the third month, the patient had no complaints of hypoglycemia, and the blood glucose was 81 mg/dL, insulin was 460 µIU/mL, and AIA was 24 U/mL. Therefore, the prednisolone dose was reduced to 0.25 mg/kg. During the control visit in the sixth month, the patient had no complaints of hypoglycemia, and the blood glucose was 87 mg/dL, insulin was 16 µIU/mL, and AIA was 2 U/mL, following which, the steroid treatment was stopped. The patient is undergoing an outpatient clinic check every six months, and no hypoglycemic complaints have been made so far.

Case 2
A 67-year-old diabetic female presented to the endocrine outpatient clinic with frequent hunger pains, tremors, and fatigue. She had diabetes mellitus for over three years and was on metformin therapy (1 g, twice daily). She had no history of sulfonylurea or insulin use and was receiving ALA therapy (600 mg, once daily) following a diagnosis of diabetic peripheral neuropathy over three months before. After starting ALA therapy, she reported frequent hunger attacks, tremors, and sweating following fasting for more than 3 h. The height, weight, and BMI were recorded as 80 kg, 160 cm, and 31.2 kg/m², respectively. The physical examination indicated no abnormal findings or acanthosis nigricans. The biochemical analysis revealed the following: glucose 55 mg/dL, insulin 670 µIU/mL (3-17), C-peptide >20 ng/mL (0.9-7.1), and HbA1c 6.4%. Hepatic, renal, and thyroid functions, pituitary hormones, complete blood count, ESR, and CRP were all normal. Protein electrophoresis was normal and serological tests for autoimmune disorders and vasculitis were negative. A prolonged fasting test was performed, and at the 8th hour of the test, she developed sweating, chills, and palpitations. The following results were recorded: blood glucose 40 mg/dL, insulin 575 µIU/mL (3-17), C-peptide >20 ng/mL (0.9-7.1), and urine ketone was negative. Glucagon stimulation test detected an increase of over 25 mg/dL in blood glucose. Sulfonylurea was absent. No pancreatic abnormality was found by abdominal CT scan, abdominal MR imaging, endoscopic sonography, or Gallium 68 PET/CT scan. The AIA level was 57 U/mL (<0.4) (Table 2). HLA typing was DRB1 04:06. Based on these findings, the patient was diagnosed with AIAS, following which ALA and metformin therapies were withdrawn, and a diet comprising complex carbohydrates was recommended. During follow-up, hypoglycemic complaints were resolved spontaneously. The patient was discharged after recommending polyclinic control. During the control visit in the first month, the hypoglycemic complaints were completely resolved with the following results: glucose 125 mg/dL, insulin 170 µIU/mL, AIA 22 U/mL, and HbA1c 7.2%. A diabetic diet was recommended. During the control visit in the third month, glucose, insulin, anti-insulin antibody, and HbA1c values were 141 mg/dL, 40 µIU/mL, 6 U/mL,

|                         | ALA treatment | ALA stopped, 1 month | ALA stopped, 3 months | ALA stopped, 6 months |
|-------------------------|--------------|----------------------|----------------------|----------------------|
| Glucose (70-100 mg/dL)  | 55           | 125                  | 141                  | 95                   |
| Insulin (3-17 µIU/mL)   | 670          | 170                  | 40                   | 16                   |
| Anti-insulin antibody (<0.4 U/mL) | 57          | 22                   | 6                    | <0.4                 |

ALA: Alpha-lipoic acid.
and 7.5%, respectively. There were no hypoglycemic attacks, and the postprandial blood glucose levels were observed to be above 180 mg/dL on ambulatory blood glucose monitoring; thus, metformin therapy was re-commenced. During the control visit in the sixth month, laboratory tests revealed the following results: blood glucose 99 mg/dL, insulin 16 µIU/mL, AIA <0.4 U/mL, and HbA1c 6.9%. The levels of blood glucose were regulated without hypoglycemia or hyperglycemia in ambulatory blood glucose monitoring.

Case 3
A 46-year-old male patient presented with fatigue, palpitation, hand tremors, and sweating for over three weeks, which would be resolved after ingestion of food. He had no history of diabetes mellitus or the use of anti-diabetic drugs or insulin. Seven weeks ago, he had started using ALA (600 mg) following the diagnosis of carpal tunnel syndrome. Patient height, weight, and BMI were recorded as 78 kg, 175 cm, and 25.46 kg/m², respectively. The physical examination showed no abnormal findings or acanthosis nigricans. Biochemical analysis revealed the following: glucose 52 mg/dL, insulin 2577 µIU/mL (3-17), C-peptide >20 ng/mL (0.9-7.1), and HbA1c 5.7%. Hepatic, renal, and thyroid functions, pituitary hormones, complete blood count, ESR, and CRP were all normal. Protein electrophoresis was normal and serological tests indicated no autoimmune disorders and vasculitis. A prolonged fasting test was performed, and on the 10th hour of the test, the patient developed sweating and chills, and the following results were recorded: blood glucose 46 mg/dL, insulin 1460 µIU/mL (3-17), and C-peptide >20 ng/mL (0.9-7.1), while urine ketone was negative. The glucagon stimulation test was performed, and an increase in blood glucose by over 25 mg/dL was detected. No pancreatic abnormality was observed in the abdominal CT scan, abdominal MR imaging, endoscopic sonography, or Gallium 68 PET/CT scan. The AIA level was 82.5 U/mL (<0.4) (Table 3). HLA typing was DRB1 04:03. Based on these findings, the patient was diagnosed with AIAS, and ALA therapy was withdrawn. The patient was given acarbose (50 mg, 3×1), and a diet comprising complex carbohydrates was recommended. Since hypoglycemic complaints persisted during follow-up, 1 mg/kg of prednisolone was initiated, which resolved the hypoglycemia. He was discharged with the recommendation of outpatient clinic control. During the control visit made in the first month, he had no hypoglycemic complaints, and laboratory tests indicated: blood glucose 70 mg/dL, insulin 1075 µIU/mL, and AIA, 53.7 U/mL. Then, the prednisolone dose was reduced to 0.5 mg/kg. He did not appear for the control visit in the third month. The patient was interviewed on the phone. It was understood that the patient’s hypoglycemic complaints had disappeared and that there had been no use of medication for the past month.

Ethical Approval All procedures performed during this retrospective study were following the ethical standards of the institutional and/ or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The ethical committee approval is not required for case reports.

Discussion
In this article, we presented three cases with AIAS developed after ALA use in Turkey. In all three cases, postprandial hypoglycemic attacks occurred along with high levels of insulin, negative imaging for insulinoma, and high levels of anti-insulin antibody, following ALA use. AIAS is a rare condition that features hyperinsulinemic hypoglycemia due to insulin autoantibodies in exogenous insulin-naive individuals (4,5). AIAS was first described in 1970 (1), and 462 cases have been reported so far. Of these cases, 82.2% were from Japan, whereas 17.0% were from the USA and Europe (2).
AIAS is currently the third-most-common cause of hypoglycemia, although its etiopathogenesis is not fully understood. AIAS is widely understood to result from the interaction of a genetic predisposition with environmental triggers, thus leading to the production of pathogenic insulin autoantibodies (7). Genetic predisposition is strongly correlated with HLA Class II, and HLA-alleles specific to AIAS are observed. The presence of HLA-DRB1×04:06 and HLA-DRB1×04:03 is a predisposition for AIAS in Asians, whereas the HLA-DRB1×04:03 allele is common among Europeans (8-10). In the cases presented in this article, the presence of HLA-DRB1×04:03 was observed in two cases, while the third case showed the HLA-DRB1×04:06 allele. Several different triggers lead to the development of AIAS, including, in the order of importance, drugs, viruses, and hematological diseases. It can stimulate the production of AIA in autoimmune disorders, such as Graves’ disease and rheumatoid arthritis (3). Several viral infections, such as measles, varicella-zoster, rubella, mumps, hepatitis, and coxsackie B, have also been reported to trigger the development of AIAS (11). AIAS may be associated with hematological disorders such as multiple myeloma or monoclonal gammapathy (12). AIAS-related drugs are mostly sulfhydryl-based, and reducing compounds play a role in the potential pathogenesis of the disease. Sulfhydryl-containing compounds may mediate the cleavage of disulfide bonds in the insulin molecule through their reducing activity; thus, increasing their immunogenicity (13). The development of AIAS, mostly after treatment with methimazole (14) and ALA (10,15), has been reported after exposure. AIAS has been described to be a type-VII hypersensitivity that is characterized by the presence of autoantibodies against a circulating antigen (16). The main pathology in the development of AIAS is the formation of the insulin autoantibody (IAA) (11), which reacts with endogenous insulin molecules. IAAs have a high binding capacity and low affinity for insulin (17,18), due to which they can bind several insulin molecules, resulting in the formation of large antigen-antibody complexes. Insulin-IAA complexes inhibit the physiological mechanisms of insulin action, resulting in low concentrations of unbound insulin and eventually transient hyperglycemia. Early postprandial hyperglycemia stimulates the secretion of insulin molecules linked to the circulating insulin-IAA complexes. The spontaneous dissociation of insulin from these complexes does not cease with the reduction of plasma glucose concentrations; thus, causing severe hypoglycemia (19,20). AIAS syndrome appears to equally affect both genders (21). Although the age of onset varies, it is mostly seen in the age range of 40-70 years (22). The previously reported case from Turkey was a 50-year-old patient (6). The age of onset of our cases was also in the 40 and 70 years, which was compatible with that reported in the literature.

ALA is a widely prescribed compound in several medical fields due to its antioxidative properties and has been used to treat diseases related to the central nervous system, polycystic ovarian syndrome, and diabetic neuropathy. It is also used in anti-aging and dietary supplements. ALA is a safe and potent agent that is used in the treatment of diabetic peripheral neuropathy and contains a sulfhydryl compound. Following oral intake, ALA cleaves into two sulfur atoms and is reduced to sulfhydryl dihydrolipoic acid, which in turn decreases oxidative stress in the peripheral tissues (3). In the literature, 17 cases with AIAS following ALA use have been reported from Japan, whereas two have been reported from Korea from Italy since 2003 and 1 from Turkey (2,6). In the cases in our study, AIAS was developed following ALA use.

AIAS often presents with hypoglycemia, which may be postprandial, post-absorptive, or fasting. Most patients have postprandial hypoglycemia, although several cases have also been reported to present with fasting hypoglycemia (23,24). Our first case had fasting hypoglycemia, whereas the second and third cases had postprandial hypoglycemia.

In most patients with AIAS, the disease resolves spontaneously within 1-3 months. However, there are cases where hypoglycemia had continued for over a year (25). Spontaneous remission occurred in approx-
imately 82% of the 197 patients that were diagnosed with IAS between 1970 and 1992 (4).

Dietary changes are recommended before pharmacological treatment to prevent the development of hypoglycemic attacks. Small frequent meals with low-carbohydrate content are recommended to reduce early postprandial hyperglycemia, thereby reducing the stimulation of insulin secretion and preventing hypoglycemic attacks (26). Treatment with alpha-glucosidase inhibitors (acarbose) prevents postprandial hyperglycemia and is effective in reducing glycemic fluctuations in AIAS (23). Moreover, steroids may be needed in cases with insufficient response (27). Use of azathioprine, 6-mercaptopurine, or plasmapheresis has been reported in cases that are unresponsive to steroid therapy (15). In our case series, a diet containing carbohydrates and acarbose therapy resolved hypoglycemia in one case, whereas steroid use was required in the remaining two cases, although short-term steroid therapy was sufficient to resolve hypoglycemia.

In conclusion, the possibility of AIAS should be considered in the differential diagnosis of hyperinsulinemic hypoglycemia (23). More- over, steroids may be needed in cases with insufficient response (27). Use of azathioprine, 6-mercaptopurine, or plasmapheresis has been reported in cases that are unresponsive to steroid therapy (15). In our case series, a diet containing carbohydrates and acarbose therapy resolved hypoglycemia in one case, whereas steroid use was required in the remaining two cases, although short-term steroid therapy was sufficient to resolve hypoglycemia.

In conclusion, the possibility of AIAS should be considered in the differential diagnosis of hyperinsulinemic hypoglycemia in individuals with or without diabetes. ALA is widely used in the treatment of diabetic peripheral neuropathy, nutritional support, or as an anti-aging agent. However, it should be remembered that this may cause AIAS in individuals with a genetic predisposition.

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Conflict of Interest
No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions
This study is entirely author's own work and no other author contribution.

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