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Case report

Familial vitamin E deficiency: Multiorgan complications support the adverse role of oxidative stress

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ABSTRACT

Vitamin E is an essential micronutrient with relevant antioxidant and anti-inflammatory properties found in plant leaves, seeds, and products derived from their processing. Familial vitamin E deficiency is a rare inherited syndrome characterized by ataxia and peripheral neuropathy with a massive decrease in plasma vitamin E (<0.5 mg/dL). This report describes the history of two siblings suffering from ataxia with vitamin E deficiency who developed premature systemic disorders (atherosclerotic vascular disease, ischemic heart disease, and liver steatosis) in absence of relevant risk factors. The association of neuromuscular symptoms and multiorgan involvement in patients with ataxia with vitamin E deficiency has not been reported to our knowledge. The lack of an effective vitamin E activity seems to be implicated in the pathogenesis of cardiovascular, gastrointestinal, and other diseases in which oxidative stress is a risk factor.

Introduction

Ataxia with vitamin E deficiency (AVED) is a rare autosomal recessive disease characterized by a massive decrease in plasma vitamin E levels due to a mutation in α-tocopherol transfer protein (α-TTP) gene (*TTPA*) on chromosome 8q13. The clinical phenotype is similar to Friedreich's ataxia (progressive cerebellar and sensory ataxia, dysarthria, hyporeflexia, loss of vibration and positional sense, and Babinski sign). Other disorders reported less frequently are pigmentary retinopathy (more common in Japanese patients with the p.H101Q mutation), cardiomyopathy (in particular the c.744delA mutation), myopathy, pes cavus, and scoliosis [1–8].

Patients with AVED absorb tocopherols in the small intestine and include them into chylomicrons normally. Once tocopherols reach the liver, hepatic α-TTP discriminates for α-tocopherol (RRR isoform in particular), incorporates it in very low-density lipoprotein (LDL) and high-density lipoprotein (HDL) for distribution in the body and reduces its catabolism and excretion [9,10], Therefore, patients with AVED are unable to maintain plasma normal values of α-tocopherol over time. The most common mutation in the *TTPA* gene is the c.744delA mutation, which is frequently observed in Mediterranean basin and is associated with severe clinical course and early onset (3–12 y of age) [1,2,11].

Patients with AVED require a high-dose oral supplement of vitamin E for life. This treatment results in stabilization of disease progression and, if it is initiated at an early clinical stage, in improvement of ataxia and cognitive function. To our knowledge, the optimal dosage of oral α-tocopherol for patients with AVED has not been widely studied. However, the dosage commonly reported in literature ranges from 800 to 1500 mg/d [1].

Vitamin E is an essential micronutrient with relevant antioxidant and anti-inflammatory properties found in plant leaves and seeds [12,13]. Inflammatory and oxidative mechanisms are implicated in the progression of atherosclerosis and several diseases [14,15]. However, to the best of our knowledge, this is one of the few case series describing a diffuse, multisystemic involvement (cardiovascular, gastrointestinal, and hepatic disorders) in humans with AVED to date.

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Case description

In 1990, a 38-y-old man with a history of progressive ataxia of the trunk and limbs, dysarthria, and head titubation since adolescence underwent neurologic consultation. Physical examination showed a wide-based irregular unsteady gait, areflexia of the lower limbs, and bilateral Babinski sign. Strength, tone, and muscular trophism were preserved. Electromyographic investigation showed normal conduction and no evidence of amyotrophy; brain magnetic resonance imaging was normal (no cerebellar involvement). Plasma α-tocopherol was very low (0.1 mg/L with significant deficiency being <3 mg/L). Genetic testing ruled out Friedreich's ataxia (no frataxin gene mutation) and detected a homozygous c.744delA mutation in the *TTPA* gene. Consequently, the diagnosis of AVED was given. Simultaneously, an oral supplementation with all racemic α-tocopheryl-acetate (Ephynal 300 mg twice daily; i.e., 7 mg/kg body weight) was initiated. The patient strictly adhered to the prescribed therapy, and the subsequent measures of plasma α-tocopherol ranged between 10 and 20 mg/L. Complementary investigations pointed out a concentric myocardial hypertrophy, in the absence of significant electrocardiographic alterations, and liver steatosis.

In 1996, the patient developed obstructive sleep apnea syndrome: Polysomnography and spirometry showed modest alveolar hypoventilation, slight obstructive disease, and weakness of the respiratory muscles. In 2005, at 53 y of age, the patient had an ST segment elevation myocardial infarction (critical three vessel coronary artery disease) and was treated with angioplasty (double stenting). In the same year, after a positive fecal occult blood test, a colonoscopy identified a small polypoid sigmoid colon cancer, which was treated successfully with laparoscopic resection. In 2010, spirometry showed a worsened mixed deficit and polysomnography detected many episodes of severe oxygen desaturation; therefore, non-invasive intermittent positive pressure ventilation was prescribed. A chest radiograph pointed out the increased transparency of the lungs. In the same year, an abdominal ultrasonography confirmed liver steatosis. Finally, in 2011, supra-aortic vessels ultrasound Doppler highlighted a bilateral carotidal intima-media thickening (right common carotid: 1.5 mm; left carotid: 1.2 mm; Fig. 1A). Notably, the patient never smoked and assumed a well-balanced diet rich in fiber and vegetables. He did not have dyslipidemia at the time (total cholesterol 4.2 mmol/L, LDL cholesterol 2.68 mmol/L, HDL cholesterol 0.85 mmol/L, lipoprotein α = 25 mg/L), the homocysteine plasma level was low (7.2 μmol/L), and C-reactive protein was 5.6 mg/L (reference value <6 mg/L). Complete blood count, prothrombin time, partial thromboplastin time, creatine phosphokinase, lactate dehydrogenase levels, uric acid, ions, kidney/liver/pancreas function tests, thyroid hormones, protein profile, urinary tests were normal. He did not have a familial history of cardiovascular diseases. The only risk factors were mild hypertension (blood pressure 135/80 mm Hg), well-controlled type 2 diabetes (treated with oral hypoglycemic agents), sedentary lifestyle, and overweight (90 kg, body mass index 29.6 kg/m^2) owing to his motor disorder. In 2005, during vitamin E supplementation, his malonyl-dialdehyde plasma level was within the reference range (0.10 μmol/L).

The patient's sister developed similar neurologic symptoms after adolescence. At 45 y of age (in 1990), the diagnosis of AVED was made and she started an integrative oral supplementation with α-tocopheryl-acetate (300 mg twice daily). She had a concentric myocardial hypertrophy and liver steatosis at diagnosis. In 2008, at 63 y of age, she had an ST segment elevation myocardial infarction, which was treated with angioplasty and stenting. In 2010, abdomen ultrasonography confirmed the presence of liver steatosis (Fig. 1B). The patient, despite her brother's respiratory and oncologic diseases, refused to undergo colonoscopy and spirometry. She also did not smoke, assumed a well-balanced diet, and did not have either hypertension or diabetes.

Discussion

This case report focused on the history of two siblings affected by AVED with a manifestation that involved more than just the nervous system. Other disorders reported in literature include cardiomyopathy, myopathy, and retinopathy [1–8]. Even if hepatic, vascular, and several dysfunctions have been described in animal models, our observation is one of the few reports describing a diffuse, multisystemic involvement (cardiovascular, gastrointestinal, and hepatic disorders) in humans with AVED to date [16–18].

Neurologic damage in AVED seems to be ascribed to oxidative stress [19,20]. Oxidative stress is also implicated in the development of atherosclerosis, coronary heart disease, and liver disease [14,15]. The occurrence of metabolic syndrome in the male patient is a confounding factor because it can cause atherosclerosis per se. At any rate, because the development of atherosclerotic lesions also implies oxidative stress, an incomplete availability of antioxidants may have accelerated this process. Thus, it should be mentioned that the suggested amount of α-tocopherol to counteract oxidative stress and to normalize the total radical-trapping antioxidant parameter of plasma (TRAP) is about 40 mg/kg body weight (i.e., a dosage definitely higher than that given to the patient) [21]. Indeed, the siblings with severe congenital vitamin E deficiency, whom we looked after, had neurologic, hepatic, and vascular complications (atherosclerosis), thus supporting the hypothesis that an insufficient protection from oxidative stress (in this case linked to vitamin E deficiency) may have had a pathophysiologic role in fastening or facilitating atherosclerosis.

Oral supplementation with 600 mg/d of all-racemic α-tocopheryl-acetate started in adulthood was not effective in protecting these patients. Patients with this disease require 800 to 1500 mg/d oral α-tocopherol [1]. Moreover, adults suffering from metabolic syndrome need higher vitamin E intake because of a lower bioavailability of this molecule [22]. When considering all of these issues, the amount of vitamin E given to the patient seems insufficient. As such, it should be noted that normal levels of malonyl-dialdehyde are not sufficient to exclude minor levels of oxidative stress (other markers were not measured). Supplementation beginning in early life, with a higher dosage of RRR-α-tocopherol, would possibly have been more effective.

Alternative hypotheses might explain the clinical course. The lack of an efficient inflammatory modulation owing to α-tocopherol deficiency could have promoted atherosclerosis. However, C-reactive protein was within the normal range. Vitamin E and its metabolites also have an anticoagulant activity and seem to have a regulatory role of gene expression in monocytes, endothelial cells, and smooth muscle cells. Thus, a deficit of α-tocopherol could have induced a prothrombotic state and promoted atherosclerosis by expression of endothelial adhesion molecules, macrophage migration, or smooth muscle cells proliferation [9,23].

The occurrence of cardiomyopathy in both of the siblings and of diabetes in the male patient is in agreement with a case series by Marzouki et al. [8]. The clinical phenotype seems more severe than the one observed in other patients with homozygous c.744delA mutation in the *TTPA* gene. This fact, and the variable response to vitamin E supplementation reported in patients with AVED [24], could be explained by additional dietary and environmental components or gene defects. At any rate, the siblings discussed here did not seem to have been exposed to environmental or dietary

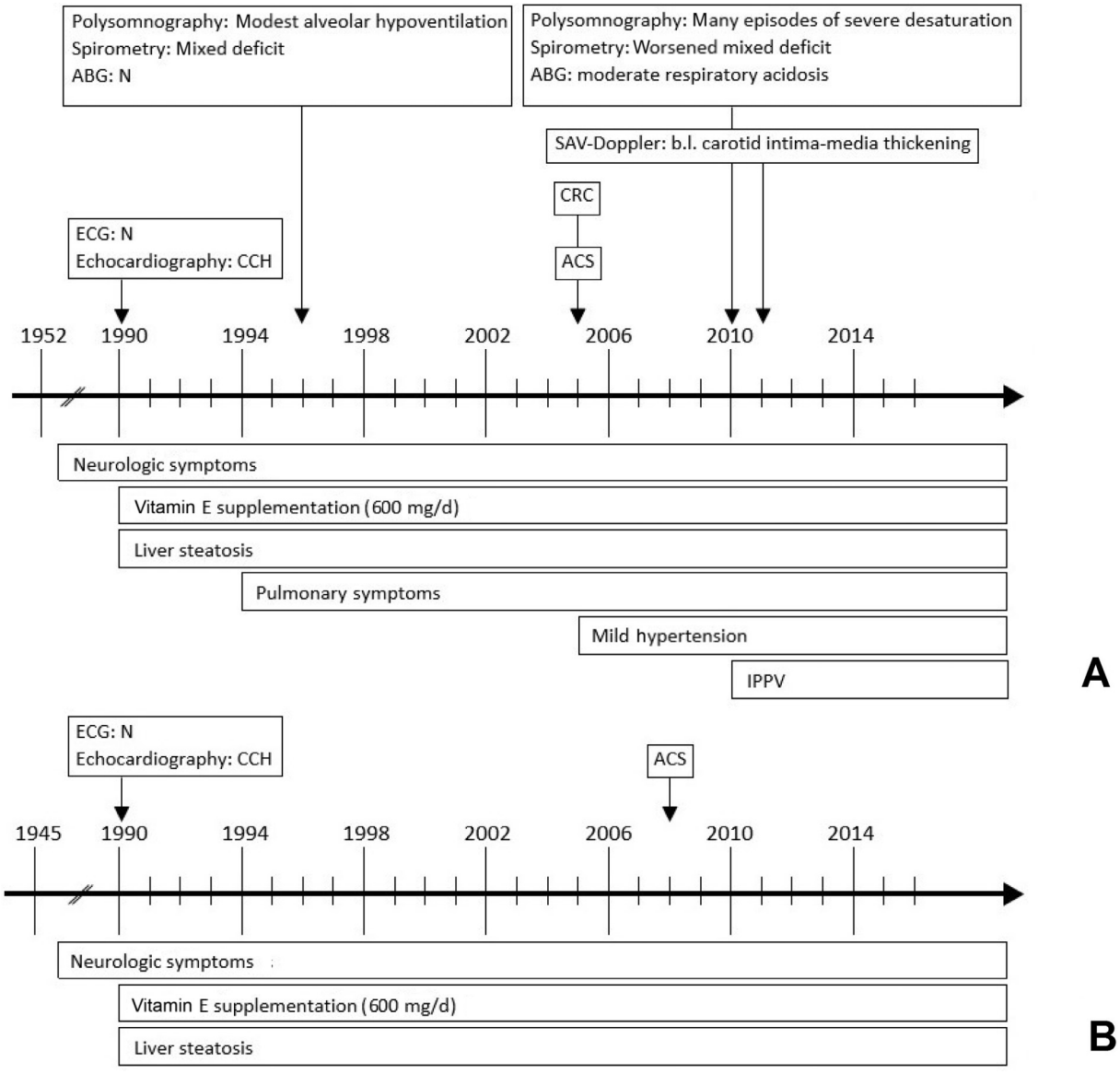

Fig. 1. Timeline of main clinical events of the two siblings: (**A**) Timeline of the brother. (**B**) Timeline of the sister. ECG, electrocardiogram; ABG, arterial blood gas; ACS, acute coronary syndrome; CCH, cardiac concentric hypertrophy; CRC, colorectal cancer; IPPV, intermittent positive pressure ventilation; SAV, supra-aortic vessels; N, in normal range.

factors that could justify the early onset of multiorgan involvement. Moreover, the few reports in literature are based on a heterogeneous population of individuals with AVED studied by different methods. Thus, it is difficult to quantify correctly the prevalence of non-neurologic complications and the responsiveness to treatment in these patients.

Conclusion

We think that these patients had a subclinical prooxidative state since adolescence because of the absence of an effective vitamin E activity. The low dose of oral α-tocopheryl acetate has contributed to the stabilization of the neurologic symptoms, whereas it seems to have had little to no effect on oxido-reductive state. The occurrence of other minor stressors (like a sedentary lifestyle or being overweight) have compromised this fragile condition, causing the clinical picture previously described. The absence of an extensive evaluation of systemic inflammatory and oxidative state does not allow us to confirm this hypothesis. It would be important, for the future, to evaluate other markers of inflammation and oxidative stress and to perform a thorough assessment (clinical and instrumental) of liver and cardiovascular system in patients with AVED.

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